Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients (Review)

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[Intervention Review]

Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

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ABSTRACT

Background

Reducing weaning time is desirable in minimizing potential complications from mechanical ventilation. Standardized weaning protocols are purported to reduce time spent on mechanical ventilation. However, evidence supporting their use in clinical practice is inconsistent.

Objectives

To assess the effects of protocolized weaning from mechanical ventilation on the total duration of mechanical ventilation for critically ill adults; ascertain differences between protocolized and non-protocolized weaning in terms of mortality, adverse events, quality of life, weaning duration, intensive care unit (ICU) and hospital length of stay (LOS); and explore variation in outcomes by type of ICU, type of protocol and approach to delivering the protocol.

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2010), MEDLINE (1950 to 2010), EMBASE (1988 to 2010), CINAHL (1937 to 2010), LILACS (1982 to 2010), ISI Web of Science and ISI Conference Proceedings (1970 to 2010), Cambridge Scientific Abstracts (inception to 2010) and reference lists of articles. We did not apply language restrictions.

Selection criteria

We included randomized and quasi-randomized controlled trials of protocolized weaning versus non-protocolized weaning from mechanical ventilation in critically ill adults.

Data collection and analysis

Three authors independently assessed trial quality and extracted data. A priori subgroup and sensitivity analyses were performed. We contacted study authors for additional information.

Main results

Eleven trials that included 1971 patients met the inclusion criteria. The total duration of mechanical ventilation geometric mean in the protocolized weaning group was on average reduced by 25% compared with the usual care group (N = 10 trials, 95% CI 9% to 39%, P = 0.006); weaning duration was reduced by 78% (N = 6 trials, 95% CI 31% to 93%, P = 0.009); and ICU LOS by 10% (N = 8 trials, 95% CI 2% to 19%, P = 0.02). There was significant heterogeneity among studies for total duration of mechanical ventilation (I^2 = 76%, P < 0.01) and weaning duration (I^2 = 97%, P < 0.01), which could not be explained by subgroup analyses based on type of unit or type of approach.

Authors' conclusions

There is some evidence of a reduction in the duration of mechanical ventilation, weaning duration and ICU LOS with use of standardized protocols, but there is significant heterogeneity among studies and an insufficient number of studies to investigate the source of this heterogeneity. Although some study authors suggest that organizational context may influence outcomes, these factors were not considered in all included studies and therefore could not be evaluated.

PLAIN LANGUAGE SUMMARY

The use of standardized protocols in weaning compared to usual weaning practice for reducing the time critically ill adult patients spend on mechanical ventilation

Helping patients to breathe with the use of a mechanical ventilator can be life saving. Yet as the duration of ventilation increases so does the likelihood of harmful effects such as (1) mechanical injury to the throat or vocal cords, (2) injury to or infection of the lungs and (3) complications of prolonged patient immobility such as clots in the legs or lungs and various infections (for example in the urinary tract). It is important therefore to recognize straight away when patients are ready to breathe for themselves so that the ventilator support can be reduced and stopped (this is known as weaning) as soon as possible. Usually weaning decisions are left to the judgement of the staff but recently protocols (or written guidelines) for weaning have been found to be both safe for patients and useful for staff. Some studies claimed that using protocols led to better practice, but there was no clear evidence that using them actually produced beneficial results for patients.

This review looked at the results of 11 studies involving 1971 critically ill patients. The studies compared the use of protocols to wean patients from the ventilator against usual practice and were conducted in America, Europe and Australia. The varied intensive care units cared for patients with heart conditions, breathing difficulties, head injuries, trauma and following major surgery. In eight studies, intensive care staff followed protocol guidelines to reduce the ventilator support; in three studies ventilator support was reduced by programmed computers according to a protocol. Overall, results showed that in comparison with usual practice, the average total time spent on the ventilator was reduced by 25%. The duration of weaning was reduced by 78% and length of stay in the intensive care unit reduced by 10%. However, these reductions were not consistent across all studies.

Among the 11 studies, there was considerable variation in the types of protocols used, the criteria for considering when to start weaning, the methods of weaning (by professionals or computers), the medical conditions of the patients and usual practice in weaning. There were insufficient studies to enable us to explore whether or not these factors were responsible for inconsistencies in individual studies. Caution will need to be applied when generalizing our findings to other intensive care units.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Patient or population: mechanically ventilated adult patients
Settings: intensive care units
Intervention: protocolized weaning
Comparison: non-protocolized weaning

Outcomes	Illustrative comparative risks* (95% CI)		Effect Estimates (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	non-protocolized weaning	protocolized weaning			
Total duration of mechanical ventilation (hours)	(a) Mean 72 hours[1] (b) Mean 144 hours[2]	(a) Mean 54 hours (43.9 to 65.5) (b) Mean 108 hours (87.8 to 131)	Geometric mean difference -25% (-39% to -9%)	1873 [10 studies]	++00 low[4]
Weaning duration (hours)	Mean 96 hours[3]	Mean 21 hours (6.7 to 66.2)	Geometric mean difference -78% (-93% to -31%)	854 [6 studies]	++00 low[5]
ICU length of stay (days)	Mean 11.2 days[3]	Mean 10.1 days (9.07 to 10.97)	Geometric mean difference -10% (-19% to -2%)	1256 [8 studies]	++00 low[6]
ICU mortality	30.7%[3]	30.3%	OR 0.98	508 [4 studies]	++00 low[7]
Reintubation	12.2%[3] (*following deliberate extubation*)	9.6%	OR 0.76	1314 [8 studies]	++00 low[8]

*The basis for the **assumed risk** (e.g. the mean control group risk) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **effect estimate** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds Ratio.

GRADE Working Group grades of evidence
High quality (++++): Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality (+++0): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality (++00): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality (+000): We are very uncertain about the estimate.

[1] The assumed risk of 72 hours comes from the average stated for short term mechanical ventilation defined by the American Association of Critical Care Nurses 3rd National Study Group on Weaning from Mechanical Ventilation (Knebel 1994). The corresponding risk is the mean or percentage that one would expect based on the effect estimates.

[2] The assumed risk of 144 hours comes from the average derived from the large epidemiological study of characteristics and outcomes in patients (N = 5183) receiving mechanical ventilation by Esteban 2002. This average was taken to represent a longer period of mechanical ventilation.

[3] The assumed risk for these outcomes comes from averages derived from the large epidemiological study of characteristics and outcomes in patients (N = 5183) receiving mechanical ventilation by Esteban 2002.

[4] Six studies had a low risk of bias. Allocation sequence generation and allocation concealment was not achieved in two studies, and unclear in one study. Risk of bias from having no, or unclear, outcome assessor blinding was present in two studies, and there was a risk of bias in two studies due to early stopping for futility. Furthernore, there was considerable variability in effect estimates (I^2 = 76%) that could not be explained by subgroup analysis. For these reasons the quality of evidence was down graded.

[5] There was considerable variability in effect estimates (I^2 = 97%) and the wide confidence intervals indicate imprecision in results.

[6] There was some of risk of bias in half the studies either in relation to allocation sequence generation and concealment, outcome assessor blinding or stopping for futility. In addition, wide confidence intervals indicate imprecision in results.

[7] There was substantial variability in effect estimates (I^2 = 57%).

[8] There was substantial variability in effect estimates (I^2 = 58%).

BACKGROUND

Prolonged mechanical ventilation for critically ill patients is associated with adverse clinical outcomes, including physiological and psychological experiences. It may, therefore, be advantageous to discontinue mechanical ventilation as soon as patients are capable of breathing independently. For the majority of patients (approximately 75%), resuming spontaneous, unassisted breathing is accomplished easily (Brochard 1994; Esteban 1995); for others it is more difficult. Patients who experience difficulty in discontinuing mechanical ventilation present significant challenges to clinicians involved in their care. These patients frequently require longer hospital stays and generally have a higher morbidity, including ventilator-associated pneumonia (Cook 1998; Papazian 1996; Vincent 1995), ventilator-associated lung injury (Meade 1995; Meade 1997; Slutsky 1998) and mortality (Dries 1997; Mancebo 1996). Moreover, ventilator-dependent patients generally remain in an intensive care unit (ICU) setting as they require specialized care and frequent monitoring. In the current climate of limited ICU bed availability, maximizing use of limited ICU resources (including nursing and equipment costs) is an important goal of providing care to critically ill patients. Thus, timely and safe discontinuation of mechanical ventilation is a desirable outcome for patients and clinicians alike.

The process leading to discontinuation of mechanical support is known as weaning. This can be generally defined as follows. "Weaning from mechanical ventilation represents the period of transition from total ventilatory support to spontaneous breathing" (Mancebo 1996). However, there are many interpretations of the 'period of transition' and the endpoint of 'spontaneous breathing'.

The transition period may take many forms, ranging from abrupt to gradual withdrawal from ventilatory support (Lessard 1996). Some clinicians do not view abrupt withdrawal as weaning and suggest the term 'discontinuation' as a better descriptor, with 'weaning' being used to describe the more gradual withdrawal process (Cook 2000; Slutsky 1993). There are differing schools of thought regarding this gradual process of weaning. Some clinicians maintain that the transition should be initiated gradually right from the outset of mechanical ventilation, with as much of the breathing workload transferred to the patient as tolerated; which obscures the onset of weaning. Other clinicians believe that the transition should only be attempted when the condition that indicated the need for respiratory support has significantly resolved. Another view is to provide full support during an initial period and then attempt to transfer the breathing workload to the patient when the patient's condition shows early signs of improvement (Marini 1995). The work of Levine and colleagues (Levine 2008) showing marked atrophy of diaphragmatic myofibrils after less than three days of ventilation would support strategies that lead to some early spontaneous breathing during the phase of mechanical ventilatory support. Gradually transferring the breathing workload requires titrating ventilatory support to the needs of the patient. Titration may mean increasing or decreasing support and may be so gradual that it leads to problems in defining the time when weaning commenced.

The end of the weaning process can be defined as the cessation of mechanical ventilation, which implies the return of spontaneous breathing, but the term spontaneous breathing is ambiguous. All forms of spontaneous breathing involve the initiation of each breath by the patient and contraction of the respiratory muscles. If the patient is free from all respiratory support (disconnected from the ventilator and extubated, or disconnected but still intubated and breathing through a T-piece circuit), the depth or size of the patient's breath will depend upon the strength and duration of respiratory muscle contraction, airways resistance and lung compliance. If the patient is still connected to a ventilator, the patient-initiated breath may be augmented by mechanical (albeit minimal) assistance from the ventilator. Both these situations are considered to be spontaneous breathing. Furthermore, some clinicians view the end of the weaning process as extubation without the need for (i) re-intubation and (ii) ventilatory support within the following 48 to 72 hours (MacIntyre 2001).

Identifying when the patient is ready to wean and deciding on the most appropriate method of weaning is influenced by the judgement and experience of the physician (Sahn 1973). Physicians tend to underestimate the probability of successful discontinuation of mechanical ventilation (Strickland 1993) and predictions, based on judgement alone, have low sensitivity (ability to predict success) and specificity (ability to predict failure) (Stroetz 1995). Until recently, there have been few standards of care in this area that are based on scientifically sound data. As a result, wide variation exists in weaning practice. There are several options, or weaning methods, for decreasing support. They include intermittent T-piece trials involving short time periods of spontaneous breathing through a T-piece circuit; synchronized intermittent mechanical ventilation (SIMV) involving gradual reductions in the ventilator rate, by increments of 1 to 4 breaths/min; pressure support ventilation (PSV) involving the gradual reduction of pressure by increments of 2 to 6 cm H_2O; spontaneous breathing through a ventilator circuit with the application of continuous positive airway pressure (CPAP) and combinations of these and newer options, such as bi-level, positive airway pressure (BIPAP). The evidence is equivocal as to which method is superior, although it has been suggested that SIMV is the least effective method (Brochard 1994; Esen 1992; Esteban 1995).

Physicians have different experiences, skills and weaning philosophies and, in view of the potential for variation, there has been an increasing interest in providing more consistent practice in ICUs by developing weaning protocols that provide structured guidance. Protocols are based on the principle that the collective knowledge of a group is usually better than that of an individual. Protocols are intended to reduce variation, to improve efficiency of practice by reducing the influence of subjectivity of judgement and experi-

ence, and by seeking to apply objectivity (Murtagh 2007). Weaning protocols are generally based on three components. The first component is a list of objective criteria based on general clinical factors used to help decide if a patient is ready to breathe without the help of a ventilator, often referred to as 'readiness to wean' criteria (such as that used by Ely 1996). The second component consists of structured guidelines for reducing ventilatory support. This may be abrupt (for example spontaneous breathing trials) or gradual by using a stepwise reduction in support to achieve discontinuation (for example SIMV or PSV), such as used by Brochard 1994; Esteban 1995; Kollef 1997; and Marelich 2000. The third component consists of a list of criteria for deciding if the patient is ready for extubation (such as that used by Hendrix 2006). In many ICUs, protocols are presented as written guides or algorithms and ventilator settings are manually adjusted by healthcare professionals. More recently, progress in ventilator microprocessor technology has enabled the development of computer-assisted management of ventilation and weaning. Computer ventilatory management adapts the ventilator output to the patient's needs using closed loop systems. These systems measure and interpret respiratory data in real time and provide continual adjustment of the level of assistance within targeted values. It is suggested that through enabling 'interaction' between the patient and the ventilator, the closed loop systems may improve mechanical ventilation tolerance and reduce the work of breathing (Burns 2008). Multiple, commercial computerized ventilation and weaning programs have been developed, including adaptive support ventilation (ASV), proportional assist ventilation (PAV) and pressure support ventilation (SmartCare/PS) (Rose 2007).

Several studies have explored the use of weaning protocols in clinical practice. Weaning protocols have been shown to be safe and effective in reducing the time spent on mechanical ventilation (Cook 2000). Notwithstanding, the evidence supporting their benefit and their use in clinical practice is not consistent across populations (Krishnan 2004; Namen 2001; Randolph 2002). The discordant results of these studies may reflect the fact that protocols vary in more ways than in composition alone. While many protocols include readiness to wean criteria and guidelines for reducing ventilator support, the criteria applied and guidance used may vary. Furthermore, not all protocols include extubation criteria. Protocols are implemented in different environments by various healthcare providers, including nurses, respiratory therapists (RTs) and physicians; and by automated (computerized) systems. Limited evidence suggests that nurses and allied health professionals may adhere to protocols more than physicians (Lawton 1999). Consequently, recent studies on the means to identify when patients are ready for weaning have compared the merits of weaning protocols led by nurses or RTs with traditional or physician-directed weaning (Ely 1996; Kollef 1997; Marelich 2000).

In addition to weaning protocols, another key feature in the management of weaning is the use of sedation and analgesia. Sedation management is known to influence the duration of mechanical ventilation. Recent clinical trials evaluating sedation protocols (Brook 1999), daily interruption of sedatives (Kress 2000) and intermittent use of sedatives (Carson 2006) have also reported reductions in the duration of mechanical ventilation and ICU stay. However, it is beyond the scope of this review to include sedation protocols.

This review will identify, critically appraise and synthesize the best current evidence supporting use of weaning protocols compared to non-protocolized practice in weaning critically ill adults from invasive mechanical ventilation.

OBJECTIVES

The first objective of this review was to compare the total duration of mechanical ventilation of critically ill adults who were weaned using protocols versus usual (non-protocolized) practice.

The second objective was to ascertain any differences between protocolized and non-protocolized weaning in terms of the following secondary outcomes.

A. Mortality.

B. Adverse events (such as re-intubation, self-extubation, ventilator-associated pneumonia (VAP) using authors' definitions).

C. Quality of life as defined by the authors.

D. Weaning duration.

E. ICU and hospital lengths of stay (LOS).

The third objective was to explore, using subgroup analyses, variations in outcomes by type of ICU, type of protocol and approach to delivering the protocol (professional-led or computer-driven).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized and quasi-randomized controlled trials that compared protocolized with non-protocolized (usual) weaning practices.

Types of participants

We included critically ill adults (at least 18 years of age and over) receiving invasive mechanical ventilation with either a nasotracheal or an orotracheal tube. We excluded studies involving children,

those exploring non-invasive ventilation as a weaning strategy and studies of tracheotomized patients only.

Types of interventions

We compared two strategies to achieve discontinuation from invasive mechanical ventilation: protocolized weaning and non-protocolized weaning (or usual practice). For the purpose of this review, discontinuation was defined as the time when mechanical ventilatory support was discontinued and the patient was breathing spontaneously through a T-piece circuit or following extubation. In addition, protocolized weaning was defined as a method of limiting the duration of invasive ventilation that includes at least the first two of the following three components.

1. A list of objective criteria based on general clinical factors for deciding if a patient is ready to tolerate discontinuation of mechanical ventilation.
2. Structured guidelines for reducing ventilatory support, such as a spontaneous breathing trial or a stepwise reduction in support to achieve discontinuation (e.g. synchronized intermittent mechanical ventilation (SIMV) or pressure support ventilation (PSV)).
3. A list of criteria for deciding if the patient is ready for extubation.

We did not exclude studies that did not include formal extubation criteria as not all studies included this component; and delay in extubation may be caused by organizational factors and not necessarily by delays in weaning. Usual weaning practice was defined as the usual practice in an ICU (as stated by the authors) where no written guides were applied. Where possible, usual practice was described in the review.

Types of outcome measures

Primary outcomes

1. Total duration of mechanical ventilation (MV) (time in hours, from MV initiation to discontinuation)

Secondary outcomes

1. Mortality (as stated by the study authors)
2. Number of patients experiencing the adverse events: reintubation; self-extubation; tracheostomy; requirement for protracted MV (greater than 21 days)
3. Quality of life (as stated by the authors)
4. Weaning duration (time, as stated by the authors, from identification of weaning readiness to MV discontinuation)
5. ICU length of stay (LOS)
6. Hospital LOS
7. Cost

Search methods for identification of studies

The search was performed using the standard strategy of the Cochrane Anaesthesia Review Group of The Cochrane Collaboration. We searched the current issue of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 1), MEDLINE (1950 to January 2010), EMBASE (1988 to January 2010), CINAHL (1937 to January 2010), ISI Web of Science (to January 2010) and LILACS (to January 2010). The search strategies for each database can be found in the appendices (Appendix 1: MEDLINE; Appendix 2: EMBASE; Appendix 3: LILACS; Appendix 4: CINAHL; Appendix 5: CENTRAL; Appendix 6: ISI Web of Science).

In addition, we searched the reference lists of all identified study reports; we contacted authors for further information on ongoing trials; and we searched the meta-register of controlled trials website at http://www.controlled-trials.com.

Data collection and analysis

Trial identification

Two authors (BB, POH) independently scanned the titles and abstracts identified by electronic searching, manual searches and contact with experts. Three authors (BB, KB, POH) retrieved and evaluated the full text versions of potentially relevant studies.

Data extraction

Three authors (BB, KB, POH) independently extracted data using a modified paper version of the Cochrane Anaesthesia Review Group's data extraction form (Appendix 7). We extracted information pertaining to the study design, method of randomization, study use of allocation concealment; and reporting of the study setting and participants, inclusion and exclusion criteria, interventions and outcomes. We attempted to contact the authors of included studies if sufficient information was unavailable in the publications and to obtain missing data. Any disagreement was resolved through consultation with a fourth author (FA).

Quality assessment

BB and POH used The Cochrane Collaboration's domain-based evaluation tool for assessing the risk of bias in included studies (Higgins 2011a), in the following six domains.

1. Was the allocation sequence randomly generated?

Random allocation sequence generation included any method that used an unpredictable sequence of allocating participants to groups, such as a random table; computer-generated random numbers; throwing dice; or shuffling envelopes.

2. Was the allocation adequately concealed?

Adequate allocation concealment included central randomization (for example allocation by a central office unaware of participant

characteristics); on-site computer system combined with allocation kept in a locked unreadable computer file accessed only after the characteristics of an enrolled participant were entered; sequentially numbered, sealed, opaque envelopes or other similar approaches that ensured the person who generated the allocation scheme did not administer it.
3. Was knowledge of the allocated interventions adequately prevented during the study?
Blinding of study participants and personnel from intervention allocations after inclusion of participants was not possible in these studies; however, we ascertained whether study outcome assessors were independent from the clinical personnel delivering or supervising the assigned intervention.
4. Were incomplete outcome data adequately addressed?
5. Were reports of the study free from suggestion of selective outcome reporting?
6. Was the study apparently free from other problems that could put it at risk of bias?
Within each study we described what was reported for each domain and contacted the authors for additional information, where necessary. We evaluated the risk of bias for each domain as follows.
Low risk: criteria appropriately applied and described in the report or ascertained in communication with the primary author of the study.
Unclear: criteria not described and impossible to acquire from or clarify with the author.
High risk: criteria inappropriately applied.
Included studies were then classified into one of the following categories.
A - Low risk of bias: all criteria met.
B - Moderate risk of bias: one or more criteria unclear.
C- High risk of bias: one or more criteria not applied or met.
At each stage, BB and POH compared results.

Data analysis

BB entered the data into RevMan 5.1.2 software and POH checked data entry. We expressed treatment effect using the odds ratio (OR) for dichotomous data and mean difference (MD) for continuous data. We calculated pooled estimates of the difference in means using either the fixed-effect model (FEM) or the random-effects model (REM) depending on the degree of heterogeneity. For the continuous variables (duration of mechanical ventilation, duration of weaning, ICU and hospital LOS) the data were skewed; therefore, these data were log transformed for the primary analyses. In three studies the authors provided the means and standard deviations on the log scale (Ely 1996; Navalesi 2008; Rose 2008). In four studies where only means and standard deviations of the un-logged data were available (Kollef 1997; Piotto 2008; Simeone 2002; Strickland 1993) approximations were used to calculate the mean and standard deviation on the log scale using Method 1 in Higgins (Higgins 2008). In four studies we could only obtain outcomes reported as the median and interquartile range (Krishnan 2004; Marelich 2000; Namen 2001; Stahl 2009): we approximated the mean using the median as suggested previously (Hozo 2004) and approximate standard deviation estimates were calculated from the interquartile range on the log scale as suggested in the Cochrane Handbook (Higgins 2011b). The difference between the treatment and control groups in the mean of a variable on the log scale was exponentiated to give the ratio of geometric means of the variable on the un-logged scale. This was generally reported as a percentage increase (or reduction) in geometric mean in the treatment group compared with the control group for ease of understanding (see Bland 1996 for more details). We informally evaluated the degree of heterogeneity by visual inspection of forest plots and more formally by measuring the impact of heterogeneity using the I^2 statistic (I^2 > 50%: significant heterogeneity); we tested it using the Chi^2 statistic ($P < 0.05$) (Higgins 2002).

Sensitivity analysis

A priori, we planned a sensitivity analysis to assess the impact of excluding studies with a high risk of bias (that is those in which there was a high risk of bias in one or more of the six domains) on the total duration of mechanical ventilation and weaning duration. In addition, we conducted a further sensitivity analysis to show the results using the un-logged data.

Clinical heterogeneity

We evaluated clinical heterogeneity (differences in the studies in relation to type of ICU, clinician(s) involved in weaning and the protocol used to guide the weaning process) using clinical judgement. We calculated pooled summary estimates of effect only in the absence of clinical heterogeneity.

Subgroup analyses

We planned to perform subgroup analyses to assess the impact of type of ICU, type of protocol and approach to delivering the protocol (physician-led, non-physician led or computer-driven) on the total duration of mechanical ventilation and weaning duration. We could only perform subgroup analyses on the impact of type of ICU measuring total duration of mechanical ventilation because only six studies reported the weaning duration. Consequently, subgroups were too small for meaningful analysis. Additionally, it was not feasible to undertake subgroup analyses on the approach to delivering the protocol for the three subgroups because it was unclear in three studies whether delivery was physician or non-physician led. Therefore we combined these subgroups and called them professional-led. We then performed the analysis on two subgroups (professional-led and computer-driven approach). In addition, we did not undertake subgroup analyses for type of protocol because five studies used a mix of two to four types of weaning protocol in their intervention groups and only two studies used the same protocol.

Assessment for publication bias

We constructed funnel plots (trial effect versus standard error) to assess possible publication bias when sufficient (at least five) studies were identified (Egger 1997).
We conducted all analyses using Review Manager (RevMan 5.1.2).

RESULTS

Description of studies

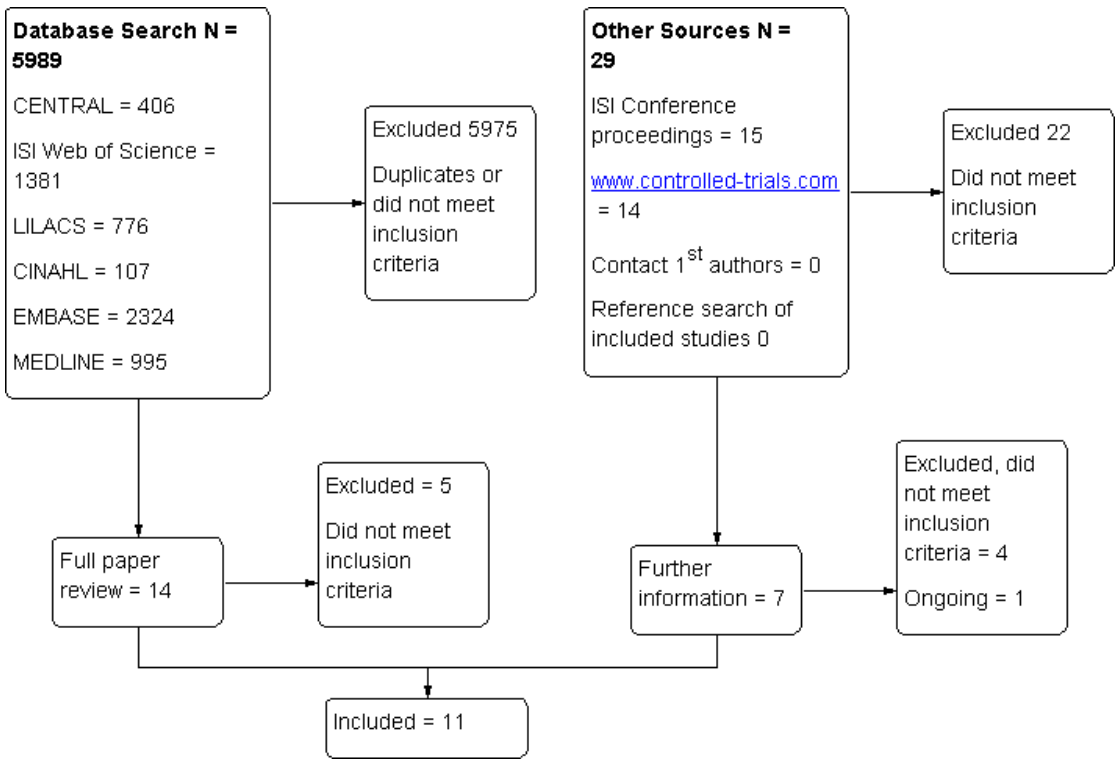
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The studies were randomized or quasi-randomized controlled trials conducted on mechanically ventilated adult patients in intensive care units (ICUs). The intervention groups were weaned following written or automated weaning protocols delivered by healthcare professionals or computer systems. The control groups were weaned according to the subjective judgment of healthcare professionals without the use of written, formal guidelines.

Results of the search

The search of electronic databases retrieved a total of 6018 citations: 5989 references from the database search and 29 relevant references from web-based sources. After reviewing the titles and abstracts, we identified and retrieved for review 14 database references in full text and obtained further information on seven unpublished trials that we located on the controlled trials website (*see* Figure 1).

Figure 1. Study flow diagram.



Included studies

We included in this review 11 studies with 1971 participants, which are described in the Characteristics of included studies table. The individual studies involved sample sizes of 15 to 357 participants and took place in intensive care units in hospital set-

tings. The majority of trials were conducted in America: six in the USA (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Strickland 1993); one in Brazil (Piotto 2008); two in Italy (Navalesi 2008; Simeone 2002;); one in Germany (Stahl 2009) and one in Australia (Rose 2008). Participants were recruited from a variety of ICUs including medical (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Strickland 1993); coronary (Ely 1996; Piotto 2008); surgical (Kollef 1997; Stahl 2009); surgical and trauma (Marelich 2000); mixed (including medical, surgical and trauma patients) (Rose 2008); neurosurgical (Namen 2001; Navalesi 2008); and cardiac surgical (Simeone 2002) units. Three trials were conducted in multiple units (Ely 1996; Kollef 1997; Marelich 2000) and seven in single units (Krishnan 2004; Navalesi 2008; Piotto 2008; Rose 2008; Simeone 2002; Stahl 2009; Strickland 1993). One trial specified the population (neurosurgical) rather than the unit (Namen 2001).

Only four studies provided the ventilatory modes used as 'usual practice' in the control group and these involved a reduction in respiratory rate in SIMV and a reduction in pressure support in PSV (Piotto 2008, Strickland 1993); a reduction in PEEP and PSV (Rose 2008); and a reduction in PSV (Stahl 2009). The remaining seven studies described usual practice as weaning according to the physician's discretion but did not describe what this constituted. A printed standard approach to ventilatory management was used to guide usual practice in the surgical and trauma unit in the Marelich 2000 study; the author was unable to provide further information on the ventilatory mode used or compliance with its use.

The approach to delivering the protocol was by registered nurse (RN) and respiratory therapist (RT) in four studies (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000); by RT in one study (Namen 2001); by physician, RN and RT in one study (Navalesi 2008); computer-driven in three studies (Rose 2008; Stahl 2009, Strickland 1993); and unclear or not stated in two studies (Piotto 2008; Simeone 2002).

All studies used readiness to wean criteria for protocol entry, but the criteria varied greatly. They ranged from a list of five to 19 criteria and the measurement parameters were not consistent among studies. All studies included criteria that measured oxygenation (namely PaO^2 and FiO^2), but they may or may not have included criteria relating to cardiovascular, neurological, inflammatory response, medication or other factors (see Table 1). The frequency of assessing readiness to wean ranged from twice daily (Marelich 2000); daily (Ely 1996; Krishnan 2004; Namen 2001; Navalesi 2008; Piotto 2008); or was stated as inclusion or protocol entry criteria (Kollef 1997; Simeone 2002; Rose 2008; Stahl 2009, Strickland 1993). In addition to the wide variety in ways of assessing readiness to wean, there were considerable differences in the weaning methods (see Table 2). In three trials the intervention was delivered by a computer-controlled weaning system: Rose 2008 and Stahl 2009 used an automated computerized protocol delivered by Draeger EvitaXL ventilator with SmartCare^{TM}/PS software that titrated pressure support (PS) and initiated spontaneous breathing trials (SBTs), and Strickland 1993 used an early computer prototype (Supersport model 2) that titrated respiratory rate and PS. Six studies used a protocolized weaning intervention that included a SBT (Ely 1996; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Piotto 2008). For patients who were ventilated for more than 72 hours, Marelich 2000 also used a stepwise reduction in PEEP, SIMV and PS prior to the SBT. Two trials used weaning protocols consisting of stepwise reductions in SIMV and PS with extubation (Piotto 2008, Simeone 2002). Because Kollef 1997 implemented the protocols in four ICUs a number of different protocols were used: SBT and extubation; SIMV reduction and extubation; and PS reduction and extubation. SBT methods and the lower parameters stated by authors as endpoints prior to discontinuation or extubation varied greatly among trials. The duration of SBTs ranged from 30 to 120 minutes, through a T-tube or ventilator circuit with continuous positive airway pressure (CPAP) ranging from 2 to 5 cm H_20 with or without PS of 6 or 7 cm H_20. In PS weaning protocols, PS was reduced to levels ranging from 4 to 8 cm H_20 prior to extubation. In SIMV weaning protocols there was a reduction in respiratory rate to rates of between 0 and 6 breaths/minute prior to SBT or extubation. In automated weaning protocols PS was reduced to levels between 5 or 7 cm H_20 and SIMV to 2 breaths/minute.

All studies, with the exception of Strickland 1993, reported on the review's primary outcome measure, total duration of mechanical ventilation. Strickland's data collection was limited to 48 hours because the trial tested a computerized protocol and only one computer system was available for the study. Only one study reported time from discontinuation from mechanical ventilation to extubation (Piotto 2008), and no study reported quality of life.

Excluded studies

We excluded nine studies. Six studies (Beale 2008; Donglemans 2009; Lellouche 2006; Papirov 2008; Scholz 2008; Taniguchi 2009) did not meet our inclusion criteria because they compared automated (computerized) protocolized weaning with standardized weaning guidelines as opposed to 'no guidelines'. In addition, East 1999 and McKinley 2001 evaluated automated (computerized) protocolized weaning in a population of adult respiratory distress syndrome (ARDS) patients using a cluster randomized controlled trial. From the papers, we were unable to identify the comparator or the weaning outcomes and we were unable to contact the authors to obtain further information. One trial received funding but was not completed due to recruitment problems and the data were unobtainable (Butler 2007). See the Characteristics of excluded studies table.

Ongoing studies

We identified one ongoing trial (Reardon 2009) which was scheduled for completion in late 2009.

Risk of bias in included studies

We used The Cochrane Collaboration's domain-based evaluation table provided in RevMan 5.1.2 to assess the validity and quality of the included trials. Most of the trials had low risk of bias across the six domains (*see* Figure 2). In eight trials, the allocation sequence was adequately generated and concealed (Ely 1996; Kollef 1997; Marelich 2000; Navalesi 2008; Rose 2008; Simeone 2002; Stahl 2009; Strickland 1993). Two trials used inadequate allocation generation and concealment: one allocated using odd and even hospital numbers (Krishnan 2004); and one allocated sequentially on recruitment (Piotto 2008). The remaining trial did not report the method used and an attempt to obtain this information from the authors was unsuccessful (Namen 2001). Given the nature of the intervention, blinding of participants and personnel to the intervention was not feasible; however, we assessed the risk of bias depending on whether or not outcome assessors were independent from those involved in patient care management decisions. In seven trials the outcome assessors were independent from the individuals administering the intervention. This was confirmed in publications (Kollef 1997; Strickland 1993) and through personal communication with authors (Ely 1996; Marelich 2000; Navalesi 2008; Rose 2008; Simeone 2002; Stahl 2009). Blinding of outcome assessors was unclear in one study (Krishnan 2004), they were not in one study (Piotto 2008) and could not be confirmed in one study despite attempts to obtain this information (Namen 2001). In the majority of trials the outcome data were reported: in two trials there was insufficient reporting of recruitment, attrition and exclusion to permit judgement (Piotto 2008; Simeone 2002). Eight trials published the weaning protocol (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Piotto 2008, Strickland 1993) and two described the automated computer system (Rose 2008; Stahl 2009) and reported all pre-specified outcomes. One trial published the weaning algorithm but did not pre-specify outcomes so there was insufficient information to permit a judgement (Simeone 2002). Seven trials appeared free from 'other sources of bias' as determined in The Cochrane Collaboration's domain-based evaluation (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Navalesi 2008; Rose 2008; Strickland 1993), two were stopped early for futility (Namen 2001; Stahl 2009), one reported unsubstantiated findings (Simeone 2002) and one is unpublished so there was insufficient information to permit a judgement (Piotto 2008). A priori sample size calculations were conducted in five studies (Kollef 1997; Namen 2001; Navalesi 2008; Piotto 2008; Stahl 2009, power calculations were mentioned but were unclear in two studies (Krishnan 2004; Marelich 2000) and were not stated in four studies (Ely 1996; Rose 2008; Simeone 2002; Strickland 1993). The judgement on the classification of risk of bias is shown in Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

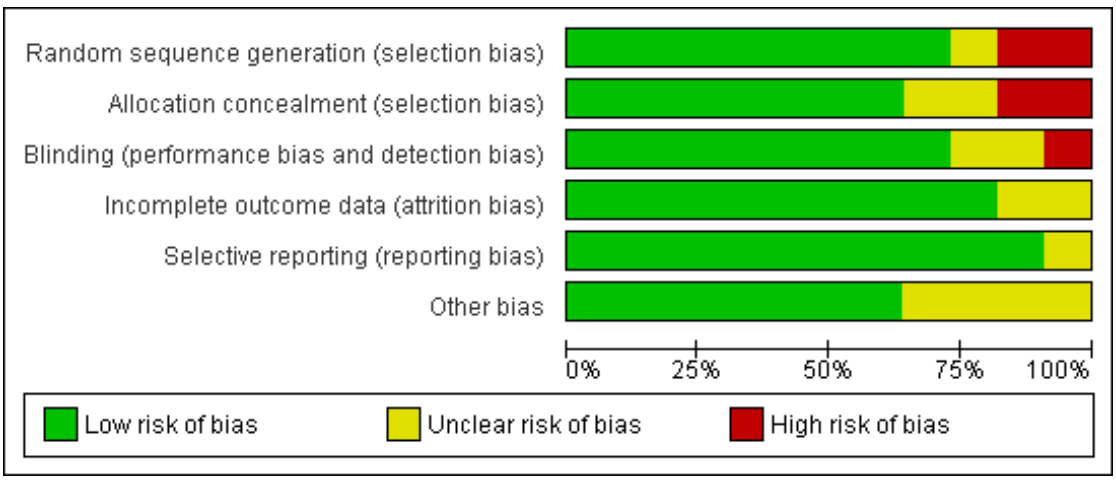
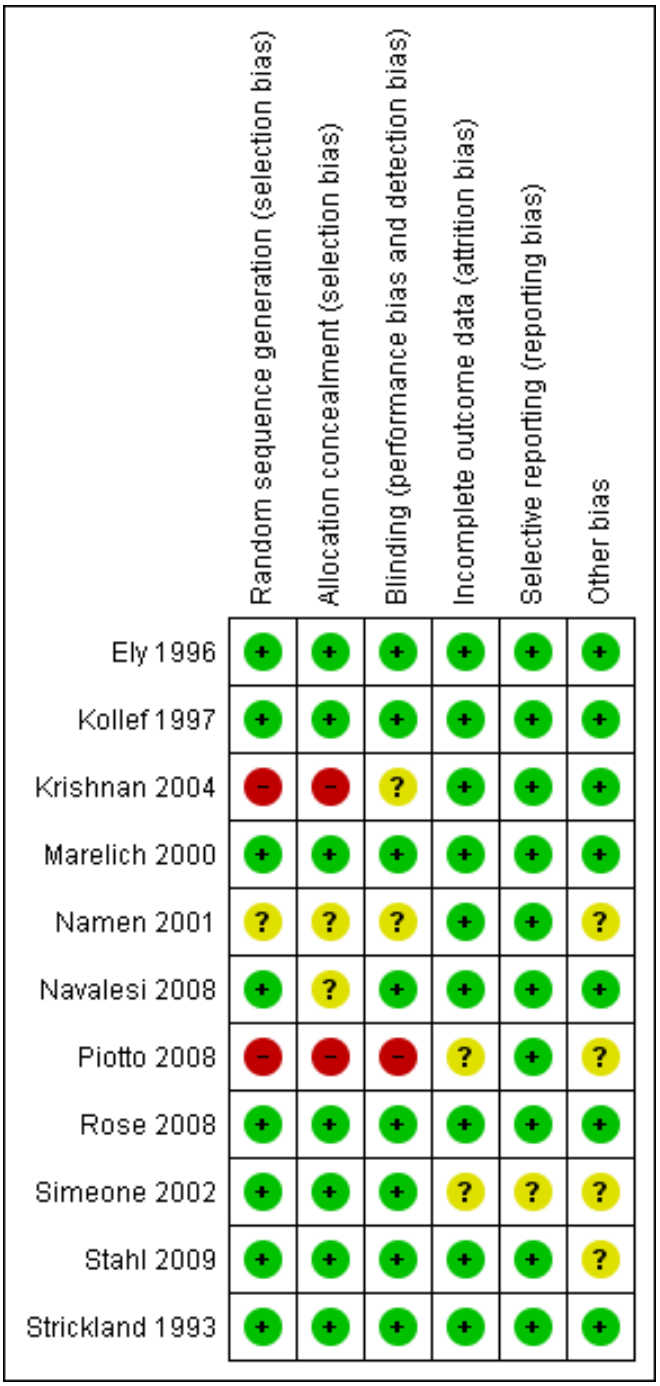


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison**

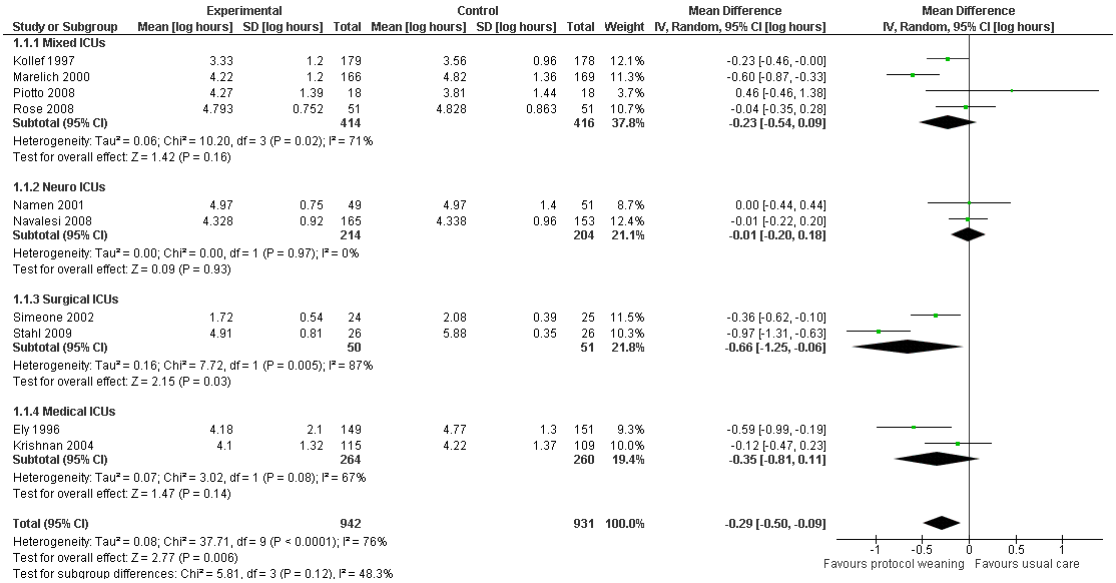
All study authors were contacted to confirm and supplement, where needed, information related to study methods and data. Ten study authors responded (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Piotto 2008; Rose 2008, Simeone 2002; Stahl 2009) and one could not be contacted (Strickland 1993). The results are presented in three sections. In section one, we present the primary analysis using log-transformed data from the 11 studies for: total duration of mechanical ventilation, weaning duration, ICU and hospital LOS. The rationale for presenting the logged data in the primary analysis is because the distributions of these outcome variables were skewed and transformations assisted in reducing the skewness. Within this section, subgroup analyses are presented where relevant. In section two, we present a sensitivity analysis of the logged data for duration of mechanical ventilation and weaning duration that excludes the studies at high risk of bias (Krishnan 2004; Piotto 2008). In section three, we present a further sensitivity analysis using un-logged data for total duration of mechanical ventilation, weaning duration, ICU and hospital LOS for all studies; that is, the data are presented in mean and standard deviation prior to log-transformation. We present this sensitivity analysis to show the effects without log-transformation.

Section 1. Primary analysis: comparison of protocolized versus non-protocolized weaning

Total duration of mechanical ventilation

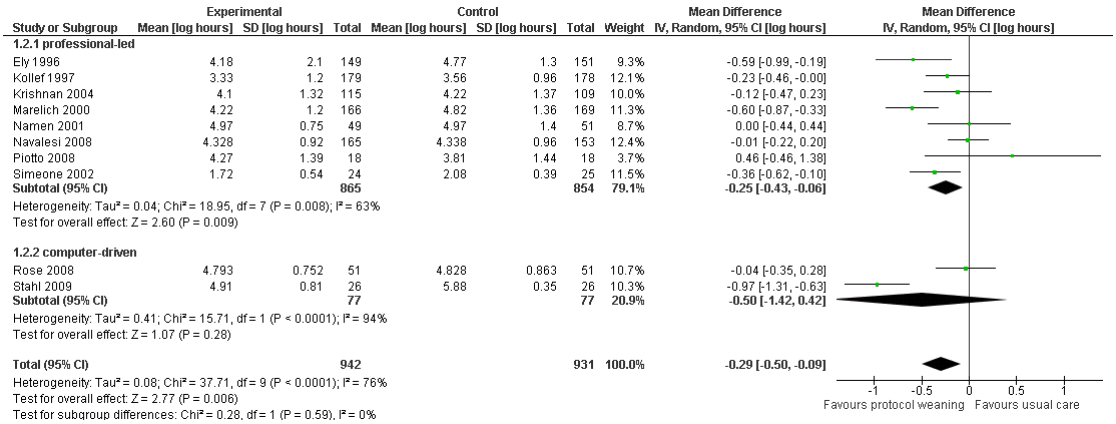
Total duration of mechanical ventilation was reported in 10 trials (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Piotto 2008; Rose 2008; Simeone 2002; Stahl 2009); one trial (Strickland 1993) did not report this outcome measure as the trial lasted only 48 hours for each individual patient. The pooled result for duration of mechanical ventilation, using the random-effects model because of significant ($P < 0.0001$) and substantial heterogeneity ($I^2 = 76$ %), demonstrated that protocolized weaning significantly reduced the mean log total duration of mechanical ventilation (mean log -0.29, 95% confidence interval (CI) -0.09 to -0.5, $P = 0.006$). This corresponds to a reduction of 25% (95% CI 9% to 39%) in the geometric mean. We performed a subgroup analysis to assess the impact of type of ICU on the total duration of mechanical ventilation. The ICU subgroups were small with two to four studies in each and included: mixed ICUs that incorporated medical, surgical and trauma patients; neurosurgical ICUs; surgical ICUs; and medical ICUs. The neurological ICU subgroup was introduced post-hoc because we were unaware of these patient-specific studies prior to the protocol and their weaning progress is different to other patient groups because of neurological impairment. Pooled analysis of the four trials in the mixed ICU group (Kollef 1997; Marelich 2000; Piotto 2008; Rose 2008) showed a non-significant reduction in the mean log in the protocolized weaning group (mean log -0.23, 95% CI -0.54 to 0.09, $P = 0.16$), which corresponds to a reduction of 21% (95% CI -9% to 42%) in the geometric mean. Pooled analysis of the two neurosurgical studies (Namen 2001; Navalesi 2008) also showed a non-significant reduction in the mean log in the protocolized weaning group (mean log -0.01, 95% CI -0.2 to 0.18, $P = 0.93$), which corresponds to a reduction of 1% (95% CI -20% to 18%) in the geometric mean. The surgical ICUs (Simeone 2002; Stahl 2009) showed a significant reduction in the mean log in the protocolized weaning group (mean log -0.66, 95% CI -1.25 to -0.06, $P = 0.03$) that corresponds to a reduction of 48% (95% CI 6% to 71%) in the geometric mean; and the two medical ICUs (Ely 1996; Krishnan 2004) showed a non-significant reduction in the mean log (mean log -0.35, 95% CI -0.81 to 0.11, $P = 0.14$), which corresponds to a reduction of 30% (-12% to 56%) in the geometric mean. See Figure 4.

Figure 4. Forest plot of comparison: 1 Primary Analysis: Protocolized versus non-protocolized weaning, outcome: 1.1 Total duration of MV by type of unit.



We performed a subgroup analysis to assess the impact of type of approach: professional-led or computer-driven. The eight studies that used a professional-led approach (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Piotto 2008, Simeone 2002) showed a significant reduction in the mean log favouring the protocolized weaning group (mean log -0.25, 95% CI -0.43 to -0.06, P = 0.009), which corresponds to a reduction of 22% (6% to 35%) in the geometric mean; there was significant heterogeneity (P = 0.008, I^2 = 63 %). The two studies using a computer-driven approach (Rose 2008; Stahl 2009) showed a non-significant reduction in the mean log in the protocolized weaning group (mean log -0.5, 95% CI -1.42 to 0.42, P = 0.28), which corresponds to a reduction of 39% (-52% to 76%) in the geometric mean. See Figure 5.

Figure 5. Forest plot of comparison: 1 Primary Analysis: Protocolized versus non-protocolized weaning, outcome: 1.2 Total duration of MV by type of approach.



For this outcome, the average percentage difference in geometric mean of 25% is consistent with estimates in all subgroups in both subgroup analyses (that is it is contained within the 95% CIs). Therefore, heterogeneity cannot be explained by type of unit or type of approach.

Mortality

Mortality was reported as hospital and ICU mortality. Six studies reported hospital mortality as an outcome measure (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Stahl 2009) with no heterogeneity (0%) and no statistically significant effect (odds ratio (OR) 1.10, 95% 0.86 to 1.41, P = 0.46). Four studies reported ICU mortality (Navalesi 2008; Piotto 2008; Rose 2008; Stahl 2009) with moderate heterogeneity (I^2 = 57%, P = 0.07) and no statistically significant effect (Analysis 1.3) (OR 0.98, 95% CI 0.48 to 2.02, P = 0.96).

Adverse events

Adverse events of reintubation, self-extubation, tracheostomy and protracted weaning were reported in nine trials (Ely 1996; Kollef 1997; Marelich 2000; Namen 2001; Navalesi 2008; Piotto 2008; Rose 2008; Simeone 2002; Stahl 2009).

Reintubation was reported in eight trials (Ely 1996; Kollef 1997; Namen 2001; Navalesi 2008; Piotto 2008; Rose 2008; Simeone 2002; Stahl 2009). The pooled result, using the random-effects model because of significant heterogeneity (I^2 = 58%, P = 0.02), was not statistically significant (Analysis 1.4) (OR 0.76, 95% CI 0.40 to 1.42, P = 0.39).

Self-extubation was reported in two trials. Ely 1996 showed no statistically significant difference in reintubation rates between groups (OR 0.40, 95% CI 0.08 to 2.08, P = 0.25). Namen 2001 also showed no statistically significant difference in reintubation rates between groups (OR 0.50, 95% CI 0.09 to 2.86, P = 0.68)

Tracheostomy was reported in six trials (Ely 1996; Marelich 2000; Namen 2001; Navalesi 2008; Piotto 2008; Rose 2008). Overall, the pooled effect was not statistically significant (Analysis 1.5) (OR 0.74, 95% CI 0.45 to 1.22, P = 0.24).

Four trials reported the requirement for protracted mechanical ventilation at three different time points: > 21 days, > 14 days and > 7 days. Ely 1996 showed a significantly reduced likelihood of protracted mechanical ventilation (> 21 days) in the protocolized group (OR 0. 42, 95% CI 0.19 to 0.96, P = 0.04). Namen 2001 showed no difference in protracted mechanical ventilation (> 21 days) (OR 0.18, 95% CI 0.02 to 1.63, P = 0.21). Rose 2008 showed no difference in protracted mechanical ventilation (> 14 days) (OR 0.68, CI 0.20 to 2.31, P = 0.54); and Kollef 1997 showed no difference in protracted weaning (> 7 days) (OR 0.63, 95% CI 0.35 to 1.15, P = 0.13).

Quality of life

None of the trial authors reported on quality of life.

Weaning duration (hours)

Weaning duration was reported in six trials (Ely 1996; Marelich 2000; Piotto 2008; Rose 2008; Stahl 2009, Strickland 1993). The pooled result for weaning duration was that protocolized weaning significantly reduced the mean log by an average of 1.52 (Analysis 1.6) (mean log -1.52, 95% CI -2.66 to -0.37, P = 0.009), which corresponds to a reduction of 78% (95% CI 31% to 93%) in the geometric mean; the reduction was significant (P < 0.00001) with substantial heterogeneity (I^2 = 97%).

ICU length of stay (hours)

The ICU length of stay was reported in eight trials (Ely 1996; Namen 2001; Krishnan 2004; Navalesi 2008; Piotto 2008; Rose 2008; Simeone 2002; Stahl 2009). There was no statistical heterogeneity among studies (I^2 = 0%). Two trials (Krishnan 2004; Simeone 2002) showed a significant reduction in ICU stay in the protocolized weaning group and the others did not, but the pooled estimate was statistically significant (Analysis 1.7) (mean log -0.11, 95% CI -0.21 to -0.02, P = 0.02) and corresponded to an average percentage difference in geometric mean of -10% (95% CI -19% to -2%).

Hospital length of stay (days)

Protocolized weaning produced no significant reduction (mean log -0.01, 95% CI -0.11 to 0.1, P = 0.9) in mean hospital length of stay in four trials (Ely 1996; Kollef 1997; Namen 2001; Rose 2008). There was minimal heterogeneity (I^2 = 11%) (Analysis 1.8). This corresponded to an average percentage difference in geometric mean of -1% (95% CI -11% to 10%).

Economic costs

Three trials reported costs: two reported ICU costs (Ely 1996; Namen 2001), with no significant differences between groups (Analysis 1.9) (mean difference (MD) $3.37k, 95% CI -15.02 to 21.76, P = 0.72); and three (Ely 1996; Kollef 1997; Namen 2001) reported no difference in hospital costs (Analysis 1.10) (MD $-0.59k, 95% CI -4.67 to 3.49, P=0.78).

Section 2. Sensitivity analysis: comparison of protocolized versus non-protocolized excluding high risk of bias studies

This sensitivity analysis explored the effects of the intervention when high risk of bias studies (Krishnan 2004; Piotto 2008) were excluded. Excluding these studies did not change the effects observed in the primary analysis. Pooled results showed that protocolized weaning significantly reduced the mean log duration of mechanical ventilation by an average of 0.34 (Analysis 2.1) (mean log -0.34, 95% CI -0.57 to -0.12, P = 0.003), which corresponds to a reduction of 29% (95% CI 11% to 43%) in the geometric mean; there was significant heterogeneity (I^2 = 80%, P < 0.0001). Additionally, protocolized weaning significantly reduced the mean log weaning duration by an average of 1.64 (Analysis 2.2) (mean log -1.64, 95% CI -3.18 to -0.1, P = 0.04), which corresponds to a reduction of 81% (95% CI 10% to 96%) in the geometric mean; there was significant heterogeneity (I^2 = 97%, P < 0.00001).

Section 3. Sensitivity analysis: protocolized versus non-protocolized weaning for all studies, un-logged data

This sensitivity analysis explored the effects of the intervention on the data prior to log-transformation. In seven studies we obtained the mean and standard deviation from either the authors or the published papers (Ely 1996; Kollef 1997; Simeone 2002; Navalesi 2008; Piotto 2008; Rose 2008, Strickland 1993). In four studies where outcomes were reported as median and interquartile range (Krishnan 2004; Marelich 2000; Namen 2001; Stahl 2009), and we were unable to obtain the mean and standard deviation, we approximated these as described in the methods.

Total duration of mechanical ventilation was reported in 10 trials; Strickland 1993 did not report this outcome. The pooled result for duration of mechanical ventilation, using the random-effects model because of significant heterogeneity (I^2 = 57 %, P = 0.01), showed that protocolized weaning significantly reduced the total duration of mechanical ventilation by an average of 19.5 hours (Analysis 3.1) (MD -19.5 hours, 95% CI -35.91 to -3.10 hours, P = 0.02).

The pooled result for weaning duration, using the random-effects model because of significant heterogeneity (I^2 = 83 %, P < 0.0001), showed that protocolized weaning significantly reduced the weaning duration by an average of 39.4 hours (Analysis 3.2) (N = 6 trials, MD -39.41 hours, 95% CI -68.74 to -10.09 hours, P = 0.008).

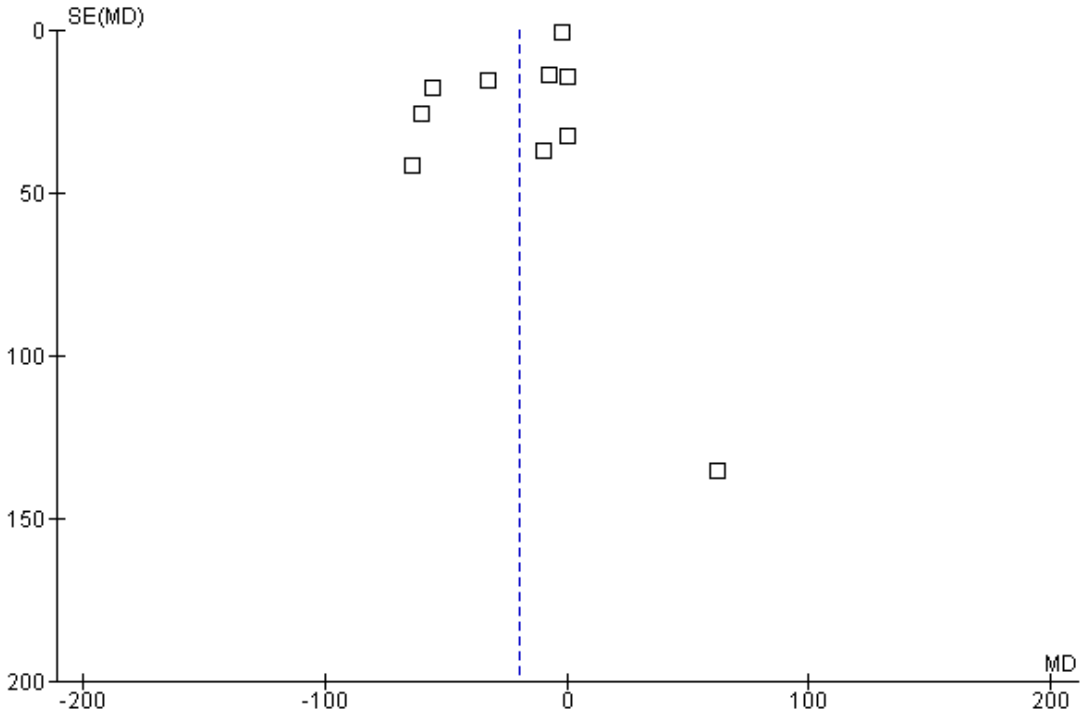
Pooled results showed that protocolized weaning significantly reduced ICU LOS by an average of 18 hours (Analysis 3.3) (N = 8 trials, MD -18.32 hours, 95% CI -30.4 to -6.25 hours, P = 0.003).

Pooled results for hospital LOS showed that protocolized weaning had no effect (Analysis 3.4) (N = 4 trials, MD -1.32 days, 95% CI -3.10 to 0.46 days, P = 0.15).

Funnel plots

Although funnel plots did not conform to the expected shape, there was little evidence of asymmetry. As we were able to obtain published and unpublished data from studies reporting both significant and non-significant statistical differences in the primary outcome measure we concluded that there was no evidence of publication or reporting bias. The non-conformity to expected shape may be due to small sample and effect sizes in some studies (*see* Figure 6).

Figure 6. Funnel plot of comparison: 1 Protocolized versus non-protocolized weaning, outcome: 1.1 Total duration of MV.



DISCUSSION

The evidence from trials of protocolized weaning to reduce the duration of mechanical ventilation in critically ill adults is derived from 11 trials which have a variety of settings, participants, interventions and outcome measures. The main outcome, duration of mechanical ventilation, was reported in 10 trials and data were available for seven out of eight secondary outcomes. Nine trials were randomized and two were quasi-randomized.The methodological quality of the studies varied from low to high.

The pooled summaries show that, when compared to usual (non-protocolized) weaning practice, protocolized weaning significantly reduces the total duration of mechanical ventilation by an average of 25% in geometric mean; weaning duration by an average of 78% in geometric mean; and ICU LOS by an average of 10% in geometric mean. Whilst the data from the pooled summaries appear beneficial, they should be viewed with caution because of the significant heterogeneity among studies, particularly in relation to the primary outcome total duration of mechanical ventilation (I^2 = 58%) and weaning duration (I^2 = 97%).

We originally planned to undertake exploratory subgroup analysis to find out if contextual factors (type of unit) or intervention factors (type of protocol or approach) were the cause of the heterogeneity. However, due to the wide variety of weaning protocols used in the included studies (only two studies used the same protocol) we only performed subgroup analyses on the impact of type of ICU (mixed, neurological, surgical, medical) and type of approach (professional-led or computer-driven).

When we explored the type of unit in relation to the duration of mechanical ventilation, we found very little statistical evidence of difference in effect within the subgroups. This may be a consequence of so few studies in each subgroup. Protocolized weaning showed a beneficial effect on total duration of mechanical ventilation in the surgical unit subgroup (Simeone 2002; Stahl 2009) but with only two trials in this subgroup, and small sample sizes (N of 49 and 52 respectively), estimates are imprecise. The pooled effect indicated that protocolized weaning was not significantly different from standard care in the mixed, neurological or medical ICU subgroups; and while both neurosurgical studies showed

no evidence of effect, there was discordance in results within the mixed and medical ICU subgroups with half the studies in these subgroups favouring protocolized weaning and half showing no effect.

Furthermore, in the subgroup analysis exploring the effect of type of approach on total duration of mechanical ventilation there was significant heterogeneity within the professional-led (I^2 = 62%) and computer-driven (I^2 = 50%) subgroups. Although the pooled summary for the professional-led subgroup showed statistically significant beneficial effects favouring protocolized weaning, the significant effect was only evident in half of the studies. Likewise, results from the two studies in the computer-driven subgroup also conflicted.

It is not easy to isolate the reasons for heterogeneity because ventilatory weaning is a complex process. It is plausible that the discordance in results among studies may be due to contextual factors (differences in patient populations and usual practice within units) or intervention factors (differences in determining readiness to wean, ventilatory modes and parameters used in weaning protocols).

Although we attempted to examine the impact of different patient populations on duration of mechanical ventilation, by exploring types of units, it was not possible to isolate patient populations in all studies because some ICUs had 'mixed' units; that is, medical, surgical, neurological and trauma patients. In addition, due to the wide variety of protocols used in included studies, it was not possible to look at the impact of specific weaning protocols on specific types of patients. Another important contextual factor, and one that causes controversy in ICU studies of non-pharmacological interventions, is the use of the 'usual care' group as a control in trials (Thompson 2007). Usual care in ICUs may encompass a wide variety of styles. For example usual care may be standardized around high level evidence and thus represent best practice, but it may also be highly variable and include unfavourable practice (Thompson 2007). Consequently, if the culture of an ICU is such that usual care is a standardized high level approach to weaning, albeit not formally laid out in guidelines, then it may not differ greatly from that delivered in a weaning protocol. Thus in a trial of effectiveness, the gap between usual care and protocolized weaning may be too narrow to show a significant difference between groups. For example, the Marelich 2000 study was conducted in one medical and one surgical and trauma ICU and the authors reported variable practice between units. The medical ICU had no standardized approach to weaning whereas the surgical ICU had a standardized approach to ventilatory management although extubation was based on subjective decisions. Thus, while combined data from both units demonstrated a reduction in the duration of mechanical ventilation time, when data were analysed separately for each unit the reduction in mechanical ventilation was only statistically significant in the medical ICU, where there was variability in weaning practice. Similarly, the study by Rose 2008 attributed their lack of effect between computer-directed weaning and non-protocolized weaning to usual practice in their ICU. They reported unlimited assessment of weaning and readiness to wean by experienced and relatively autonomous critical care nurses, a one to one nurse to patient ratio supported by 24-hour medical staff and twice-daily intensivist rounds. These examples suggest that one might not find any further beneficial effect from using weaning protocols in comparison with standardized high level approaches to weaning. A full description of usual care in the control groups was not provided in the included studies, therefore we cannot be certain that this is the case.

In relation to intervention factors, there were many methodological differences among studies that may have contributed to heterogeneity. The type and number of criteria used to determine readiness to wean within protocols varied considerably and so the leniency or restrictiveness of criteria may have contributed to the differences. In relation to the protocols themselves, of the 11 studies included in this review only two used an identical weaning protocol, consisting of a daily screen of five criteria, a 2-hour SBT on CPAP 5 cm H_20 and notifying the physician if the SBT was successful (Ely 1996; Namen 2001). Even so, they reported conflicting results in the duration of mechanical ventilation and weaning, and this may be due to differences in the type of patient population (medical and neurosurgical) and usual practice within the units.

In relation to risk of bias within studies, methodological quality ranged from low to high. The intervention could not be blinded to personnel, which is understandable. It is plausible therefore that the unblinded nature of the intervention may have prompted a change in behaviour on behalf of professionals to 'beat the protocol' or computer (Hawthorne effect) and this may have affected results.

The summary effects for ICU and hospital mortality showed no statistically significant differences between the protocolized and usual practice groups. Similarly, protocolized weaning showed no statistically significant effect on adverse events such as reintubation, self-extubation, tracheostomy and protracted weaning, but our meta-analysis had little power to investigate these outcomes because they were relatively rare events.

Basic costing exercises undertaken by Ely 1996, Kollef 1997 and Namen 2001 showed no statistically significant differences between groups, in either ICU or hospital costs. However, these fail to provide a full understanding of the true impact of protocolized weaning, including costs associated with training. A cost-effectiveness analysis would be beneficial in enabling policymakers to compare the costs associated with protocolized weaning with the benefits gained.

Sensitivity analyses

In the sensitivity analysis of low risk studies (Results, Section 2) heterogeneity and effect sizes were similar to those from the primary analysis indicating that high risk of bias studies did not adversely impact on overall results.

A limitation of the review is that in the included studies the outcomes, duration of mechanical ventilation and weaning duration, are likely to be skewed because the majority of patients spend only a few days on the ventilator while for other patients the duration of ventilation can be prolonged. Indeed, this is likely to be the reason why some authors reported median and interquartile range. In our primary analysis, the estimates are based on approximations of the data presented (as described in the methods) and this may have impacted on our analysis. However, we feel this is likely to have had negligible impact as we conducted a further sensitivity analysis of the un-logged data and this had little effect on our main findings (Results, Section 3).

Developments in the area of weaning

Applying guidelines to real-life clinical practice can be difficult because their effectiveness is dependent upon many factors including clinician acceptance of them, ICU workload, frequency of assessments, and continuing assessment and feedback to ensure compliance with them. Automated computerized systems are increasingly being employed in an attempt to improve the adaptation of mechanical support to the needs of patients. Computers can continuously monitor changes in ventilation, interpret real-time physiological changes and adapt ventilation in response to these changes. This is evident from the automated weaning studies included in this review (Rose 2008; Stahl 2009; Strickland 1993). However, in comparison with usual care of non-protocolized weaning, their efficacy in reducing the duration of mechanical ventilation has yet to be demonstrated. It should be noted that the practice of protocolized weaning has increased to the point where it is 'usual practice' in many units. As one might expect, we are beginning to see studies that compare automated weaning with protocolized weaning practice (Beale 2008; Donglemans 2009; Lellouche 2006; Papirov 2008; Scholz 2008; Taniguchi 2009).

AUTHORS' CONCLUSIONS

Implications for practice

There are several important implications for practice arising from our systematic review and meta-analysis. First, the use of protocolized weaning may result in decreased total duration of mechanical ventilation, weaning duration, and ICU length of stay. The reduction in the duration of mechanical ventilation and weaning may be due to consistent application of objective criteria for determining readiness to wean and a guided approach to reducing support. Similarly, the reduction in ICU stay may be attributable to the reduction in mechanical ventilation. It is reasonable to presume that a reduction in mechanical ventilation may lead to a reduced requirement for tracheostomy, particularly as tracheostomy is usually initiated because of protracted mechanical ventilation. However, in units where objective criteria and guided approaches are already incorporated into standard weaning practice, further beneficial effects of protocolized weaning may not be gained on these outcomes.

Implications for research

Studies included in the review varied in the details presented regarding weaning protocols and, in particular, in the degree to which they described usual practice and the settings in which they were conducted. In many studies neither usual practice nor organizational context (for example staffing ratios and frequency of medical rounds) were described in sufficient detail. Thus it is difficult to ascertain the extent to which weaning practice differed between the experimental and control groups in the individual studies. It is important that future trials fully report the details of weaning protocols, usual practice and the context into which weaning protocols are introduced as this would enable clinicians to gain a more accurate picture of the potential impact of weaning protocols in their own environment.

The use of weaning protocols is a complex intervention that has multiple interrelated and interdependent components (Blackwood 2006). Due to methodological limitations, data to support the use of weaning protocols are inconclusive to date. There is, therefore, a need for well designed clinical trials to evaluate weaning protocols. Such trials must take into account the contextual and intervention factors that are likely to impact on protocolized weaning. These need to be described in sufficient detail to enable both accurate replication and comparisons among studies. Such trials would enable clinicians to more readily generalize findings to their particular intensive care units. Furthermore, such trials must fully evaluate the components of this complex intervention by focusing on mixed methods research. Future studies of the efficacy of weaning protocols should follow a framework that incorporates process evaluation (such as that advocated by the Medical Research Council 2008) to understand how context influences outcome and to provide insights to aid implementation in other settings. In addition, an economic evaluation taking into consideration the cost effectiveness of protocolized weaning, not only from the payer's perspective but also from that of service users and society as a whole, would be useful for decision makers.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ely 1996

Methods	Randomized controlled trial
Participants	Setting: USA; 806-bed university medical centre. One medical and one coronary ICU. "Closed units staffed by intensivists". Staffing - 3.5 physician hours/bed/day (Krishnan 2004). Participants: 300 adults (149 intervention, 151 control). Conditions: CHF; heart disease; COPD/asthma; pneumonia; ARDS/MSOF; GI and liver disease; cancer/leukaemia; overdose/ketoacidosis; neurologic emergency Inclusion:18-years and older; intubated and mechanically ventilated. Exclusions: 18-years; lack of informed consent; extubation order at time of evaluation; dependence on MV 2-weeks before recruitment
Interventions	Intervention: protocol delivered by RNs and RTs consisting of daily screening of readiness to wean using 5 criteria; a 2-hour SBT; and notification of the physician of successful SBT Control: usual practice consisting of weaning according to physician judgement
Outcomes	1. Total duration of mechanical ventilation 2. Weaning duration (time from successful screening test to discontinuation of MV) 3. ICU length of stay 4. Adverse events (reintubation; self-extubation; tracheostomy; MV > 21-days) 5. Cost of respiratory care, intensive care and hospitalisation 6. Hospital length of stay 7. Mortality
Notes	Study approved by hospital Institutional Review Board and informed consent required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomization.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	"All of the data were collected by research personnel not involved in the patients' care"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using ITT principle

Ely 1996 (*Continued*)

Selective reporting (reporting bias)	Low risk	Weaning protocol is available; all pre-specified outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias. Sample size calculation not stated

Kollef 1997

Methods	Randomized controlled trial
Participants	Setting: USA, 2 medical and 2 surgical ICUs in 2 university affiliated teaching hospitals (900 and 450-beds). Nurse to patient ratio 1:2 and 4.0 physician hours/bed/day (Krishnan 2004). Participants: 357 adults (intervention 179, control 178). Conditions: post-operative; trauma; pneumonia; COPD/asthma; pulmonary oedema; respiratory failure; drug overdose; cardiac arrest/cardiogenic shock Inclusion: mechanically ventilated. Exclusions: head/facial burns or trauma; transfer from other hospital with prior MV; brain death
Interventions	Intervention: protocol entry criteria assessed, then protocol delivered by RNs and RTs consisting of: a) ICUs 1 and 4 - daily SBTs through ventilator circuit with CPAP $\leq$5cmH20 and PS $\leq$6cmH_20 for 30-60 minutes then extubation. b) ICU 2 - stepwise reductions of 2cmH_20 in PSV until 6cmH_20 then extubation. c) ICU 3 - on PEEP $\leq$5cmH_20, PS $\leq$6 cmH_20, stepwise IMV reductions of 2 breaths/min until $\leq$4 breaths/min, then 0 breaths for 30-60 minutes, then extubation Control: usual practice consisting of weaning according to physician judgement
Outcomes	1. Total duration of mechanical ventilation from intubation until discontinuation of MV 2. Reintubation 3. Length of hospital stay 4. Hospital mortality rate 5. Hospital costs. 6. MV time prior to weaning 7. Requiring MV for > 7-days
Notes	Study approved by University Human Studies Committee and hospital Institutional Review Board - both waived requirement for informed consent

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Seperate blocked randomization schedules.

Kollef 1997 (*Continued*)

Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors were independent from the individuals administering/supervising the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.Recruitment & attrition data presented. Analyses performed using ITT principle
Selective reporting (reporting bias)	Low risk	Weaning protocol is available; all pre-specified outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias. Sample size calculation stated (based on 80% power to detect a 1-day difference in weaning time, α 0.05, 145 required for each group)

Krishnan 2004

Methods	Quasi-randomized controlled trial
Participants	Setting: USA, 1000-bed hospital. 14 bed medical ICU; nurse to patient ratio 1:2; 9.5 physician hours/bed/day Participants: 299 adults (intervention 154, control 145). Conditions: cardiopulmonary arrest; pneumonia/acute lung injury; COPD/asthma; cardiogenic pulmonary oedema; neurologic emergency Inclusion: mechanically ventilated > 24-hours. Exclusions: previous participants; enrolled in other studies; transferred from other facilities intubated
Interventions	Intervention: protocol delivered by RNs and RTs consisting of daily screening of readiness to wean using 5 criteria; a 1-hour SBT on CPAP 5cmH_20; and notification of the physician of successful SBT. Control: usual practice consisting of weaning according to physician judgement
Outcomes	1. Total duration of MV (time from start of MV to beginning of SBT that ended with successful discontinuation of MV) 2. Duration of SBT that preceded MV discontinuation 3. ICU length of stay 4. Location after ICU discharge 5. ICU and hospital mortality 6. Reinstitution of MV (< 48-hours & > 48-hours)
Notes	Successful discontinuation was unassisted breathing for 48-hours Study approved by Institutional Review Board - waived requirement for informed consent
Risk of bias	

Krishnan 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Assigned by hospital number (odd versus even).
Allocation concealment (selection bias)	High risk	Case record number.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors were independent from those making decisions. RNs and RTs recorded results of screening and SBTs on case report forms. Study coordinator documented other data
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. ITT analysis performed
Selective reporting (reporting bias)	Low risk	Weaning protocol is available; all pre-specified outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias. Sample size calculation unclear (estimates based on Ely 1996 study to provide 82% power to detect a 1-day difference in MV duration, α 0.05, but number of participants required not stated)

Marelich 2000

Methods	Randomized controlled trial
Participants	Setting: USA, 1 university medical centre. 3 ICUs with medical and trauma/surgical services; RT to ventilator ratio 1:7; nurse to patient ratio 1:1 or 1:2; 4.7 physician hours/bed/day Participants: 335 adults (intervention 166, control 169). Conditions: post-operative trauma; non-operative trauma; pneumonia; neurologic emergency; poisoning; GI bleed/liver; COPD/asthma; respiratory failure; metabolic/renal; CHF Inclusion: mechanically ventilated. Exclusions: pregnancy; < 18-years; mentally disabled; prisoners
Interventions	Intervention: protocol delivered by RNs and RTs consisting of twice daily screening of readiness to wean; a 30-minute SBT (< 72-hours ventilated) or stepwise reduction in PEEP, PS and IMV (> 72-hours ventilated); and notification of the physician of successful SBT Control: usual practice consisting of weaning according to physician judgement on MICU; and a standardized MD approach on trauma services consisting of gradual reductions in IMV, then PS, then SBTs administered (but extubation was based on subjective opinion)

Marelich 2000 (*Continued*)

Outcomes	1. Total duration of MV 2. Incidence of VAP 3. Weaning duration (duration of MV from study entry to discontinuation of ventilator support) 4. Duration of MV from initiation of mechanical support to meeting discontinuation criteria 5. Ventilator discontinuation failure rate 6. Tracheostomy 7. Hospital mortality
Notes	Study approved by University Human Subjects Review Committee - requirement for informed consent waived

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified according to medical or surgical, put into envelopes and shuffled
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors independent from those involved in intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented
Selective reporting (reporting bias)	Low risk	Weaning protocol is available; all pre-specified outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias. Sample size calculation unclear (based on 80% power to detect a 1. 5-day difference in time to ventilator discontinuation, α 0.05, but numbers required not stated)

Namen 2001

Methods	Randomized controlled trial
Participants	Setting: USA. Hospital and units not specified. Staffing ratios not stated Participants: 100 neurosurgical adult patients (intervention 49, control 51) Conditions: head trauma; subarachnoid haemorrhage; intracerebral haemorrhage/arteriovenous malformation; tumour; spinal trauma Inclusion: mechanically ventilated. Exclusions not stated.

Namen 2001 (*Continued*)

Interventions	Intervention: RT-focused protocol consisting of daily screening of readiness to wean; a 2-hour SBT; and notification of the physician of successful SBT Control: not stated.
Outcomes	1. Total duration of MV 2. ICU length of stay 3. Time to successful extubation 4. Adverse events (reintubation; self-extubation; tracheostomy, MV exceeding 21 days) 5. Costs of MV, respiratory and ICU care & overall hospitalisation 6. Hospital length of stay 7. Mortality 8. Existence of pneumonia
Notes	Study approved by hospital Institutional Review Board and informed consent required

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. ITT analysis performed
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Unclear risk	Trial stopped early for futility. Study powered for 188 patients (80% power, α 0.05) to detect a 20% difference in duration of MV. Planned interim analysis at 12-months showed lack of efficacy, study stopped at 100 patients

Navalesi 2008

Methods	Randomized controlled trial
Participants	Setting: Italy, 1200 bed hospital. Closed neuro-ICU, 9 bed unit. Nurse to patient ratio 1:2; 24-hour physicians certified and trained in anaesthesiology and critical care Participants: 318 adult neurosurgical and neurological patients (165 intervention group; 153 control group) Conditions: subarachnoid haemorrhage, intracerebral haemorrhage; head trauma; cerebral tumour; spinal trauma

	Inclusion: mechanically ventilated adults between 18 and 80-years; not already intubated or transferred from other ICU; mechanically ventilated >12-hours; no continuous sedation infusion; not on controlled mechanical ventilation; ability to trigger the ventilator; no tracheostomy; no surgery scheduled for 72-hours Exclusion: lesion affecting upper airway; pre-existing decision to limit life support
Interventions	Intervention: daily readiness to wean criteria (GCS =/> 8; cough present; tracheal suctioning =/< 2/hour; normal sodium blood values; Temperature <38.5^{o}C; pH $\geq$7.35 and $PaCO_2$ $\leq$50mmHg; PaO_2/FiO_2 ratio $\geq$200 with PEEP $\leq$5cmH_2O; FiO_2 $\leq$0.4; Heart rate $\leq$125 b/min; SBP $\geq$90 mmHg without vasoactive medication); followed by a 1-hour SBT through ventilator circuit with 2-3cm$H_2$0 CPAP and FiO_2 0.4. Extubation criteria: respiratory rate/tidal volume ratio $\leq$105, PaO_2/FiO2 $\geq$200, pH $\geq$7.35 and $PaCo_2$ $\leq$50mmHg. Control: usual care that was daily evaluation by attending physician, weaning and extubation using their own clinical judgment
Outcomes	1. Rate of extubation N (%) 2. Duration of mechanical ventilation (days) 3. Length of ICU stay (mean/SD) 4. Length of hospital stay (mean/SD) 5. ICU Mortality N(%) 6. Rate of tracheostomy N(%)
Notes	Ethics committee approval; requirement for informed consent waived

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computer-generated randomization sequence was drawn up. We used a simple randomization without blocks."
Allocation concealment (selection bias)	Unclear risk	"We utilised the same PC used to register the patient in the ICU, which was located in the office of the chief nurse. As soon as the patient was eligible, a person (the chief nurse from Monday to Friday) not involved in the study (i.e. not one of the authors) communicated to the attending physician the group of assignment."
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, staff and research personnel unblinded to the intervention, "however the analysis of data were performed by two investigators not involved either in the clinical management of patients and in data acquisition and report."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition and exclusions reported. ITT analysis performed.

Navalesi 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	All a priori outcomes reported.
Other bias	Low risk	Appears to be free of other sources of bias. Sample size calculation stated (based on 80% power, α 0.05, 140 patients in each group)

Piotto 2008

Methods	Quasi-randomized controlled trial
Participants	Setting: Brazil, hospital not described. One coronary care unit. Staffing ratios not stated Participants: 36 coronary care patients (intervention 18, control 18) Conditions: myocardial revascularization; valve surgery; acute coronary syndrome; CHF; pulmonary thromboembolism Inclusion: mechanically ventilated > 24 hours. Exclusion: conditions that might result in difficulty understanding informed consent; lack of consent; end-stage diseases; dependence on MV
Interventions	Intervention: when cause of MV requirement resolved, daily assessment of clinical criteria for SBT, SBT 120-minutes delivered by RT then extubation Control: weaning according to physician and RT judgement, typically gradual reduction in ventilatory support (RR and PS) and in some cases SBT without evaluation of clinical criteria
Outcomes	1. Reintubation rate during hospitalization 2. Length of CCU stay 3. Time from intubation to start of weaning 4. Time from start of weaning to extubation 5. Time from SBT to extubation 6. Presence of respiratory infection in patients requiring reintubation 7. Mortality of patients requiring reintubation
Notes	Predetermined protocol entry criteria specified. After resolution of cause for MV resolved, all patients underwent a daily clinical evaluation according to prespecified criteria Weaning failure was return to MV in < 48-hours. Informed consent required: ethical approval not stated. Contacted the authors for clarification on random allocation sequence and concealment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	1st recruited patient into experimental group, 2nd into control group, thereafter alternated
Allocation concealment (selection bias)	High risk	Not concealed.

Piotto 2008 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	The investigator collected data and was involved in weaning the experimental group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Recruitment and attrition data absent.
Selective reporting (reporting bias)	Low risk	Study protocol is available; all pre-specified outcomes reported
Other bias	Unclear risk	Unpublished paper. Some changes made between findings presented in the paper submitted for publication and subsequent requests for information from the investigator. Sample size calculation stated (based on 80% power to detect a difference in reintubation of 15% in experimental group and 60% in control group, α 0.05, 17 patients in each group)

Rose 2008

Methods	Randomized controlled trial
Participants	Setting: Australia, 390 bed acute tertiary referral hospital with 100,000 admissions/annum. 24-bed mixed medical/surgical/trauma ICU. Nurse to patient ratio 1:1, 9 intensivists providing twice-daily structured rounds and supported by 26 hospital medical officers providing 24-hour care Participants: 102 adult patients (51 intervention group; 51 control group) Conditions: trauma; coma; post-operative; pneumonia; sepsis; heart failure. Inclusion: 24-hour mandatory ventilation; a ventilator with SmartCare/PS software ready for use; PEEP $\leq$8cmH_2O; PaO_2/FiO_2 ratio >150 or $SaO_2 \geq$90% with FiO_2 0.5; Plateau Pressure $\leq$30 cmH_2O; haemodynamic stability; temperature 36-39 C; GCS >4; no anticipated requirement for transport or surgery; successful completion of 30-min SBT using max 20cm$H_2$0 PS to achieve VT >200mL. Exclusion: ventilator with software unavailable; CNS disorder with anticipated poor outcome
Interventions	Intervention: automated computerized protocol delivered by Draeger EvitaXL ventilator with SmartCare^{TM}/PS software version 1.1. Programme monitors patient's respiratory status every 2 to 5 minutes and adjusts PS accordingly. When PS reduced to 7 cmH_2O (or 5 cmH_2O for tracheostomy), PEEP was reduced to 5 cmH_2O and following a 1-hour monitoring period patient assigned as having ventilator "separation potential" Control: weaning of PS and PEEP according to usual local practice in the absence of formal guidelines. When PS reduced to 7 cmH_2O (or 5 cmH_2O for tracheostomy) , PEEP was reduced to 5 cmH_2O and following a 1-hour monitoring period patient assigned as having ventilator "separation potential"

Rose 2008 (*Continued*)

Outcomes	1. Time to separation (immediately following successful 30-minute PS SBT [randomization] to declaring "separation potential") in hours 2. Total duration of weaning (randomization to successful extubation) 3. Time from intubation to first extubation 4. Time from intubation to successful extubation 5. Length of ICU stay 6. Length of hospital stay 7. ICU Mortality 8. Rate of successful extubation 9. Rate of reintubation 10. Rate of use of non-invasive ventilation post-extubation 11. Tracheostomy 12. Prolonged mechanical ventilation > 14-days
Notes	Ethical approval. Required written informed consent from next-of-kin and later patients (when competent)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization (block size 4) .
Allocation concealment (selection bias)	Low risk	Administered through a sequential opaque envelope technique.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, staff and research personnel unblinded to the intervention. The investigator collected data, but was not involved in patient care or management
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition and exclusions reported. ITT analysis conducted.
Selective reporting (reporting bias)	Low risk	All a priori outcomes reported.
Other bias	Low risk	Appears to be free of other sources of bias. Sample size calculation not stated

Simeone 2002

Methods	Randomized controlled trial
Participants	Setting: Italy, hospital not described. One cardiac surgical ICU. Staffing ratios not stated Participants: 49 patients >15-years of age (intervention 24, control 25) Conditions: elective coronary, aortic and mitral valve surgery Inclusion: low or medium Higgins risk score. Exclusion: $Fi0_2$ >0.5%; PEEP >10cmH_20 to achieve O_2 sat >90%; PEEP >10cmH_20;

Simeone 2002 (*Continued*)

	excessive respiratory secretions; uncontrolled arrhythmias; high inotropic support; bleeding > 250mls in first hour; contraindications to steroid administration
Interventions	Intervention: protocol consisting of reduction in SIMV and 2cmH_20 stepwise reduction in PSV until SIMV 0 and PS 4cmH_20, then extubation. Control: weaning according to physician's subjective clinical judgement without the aid of the measured indexes
Outcomes	1. Total duration of mechanical ventilation (intubation time) 2. ICU length of stay 3. Number of complications recorded (cardiac tamponade; myocardial ischaemia; increased creatinine level; aphasia; disorientation; paralysis; post-operative bleeding; reintubation due to epileptic crisis)
Notes	Patients assessed 3rd/4th hour after admission. Pre-determined protocol entry criteria specified Ethical committee approval gained and informed consent required

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used a random numbers table generated by a software program on a PC
Allocation concealment (selection bias)	Low risk	Each random number was associated with either 'control' or 'experimental' & was inserted into a black sealed envelope
Blinding (performance bias and detection bias) All outcomes	Low risk	"The fellows were involved in collecting the data, not in weaning the patient" - communication
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcomes were not pre-specified. Recruitment and attrition data absent. ITT not stated
Selective reporting (reporting bias)	Unclear risk	Outcomes were not pre-specified.
Other bias	Unclear risk	No data to support following statements; "...Patients that underwent a longer cardiopulmonary bypass time required prolonged MV support...". (Baseline showed patients in the control group had longer cardiopulmonary bypass times.) "...a weaning protocol allows early identification of patients ready for spontaneous breathing, thus reducing MV dependence." (This outcome - early identification or MV time prior to weaning - was not measured.) Data produced from a Fast Track Recovery study for comparison with weaning group data, but no information

Simeone 2002 (*Continued*)

		provided on this group of patients (nos., characteristics etc) Sample size calculation not stated.

Stahl 2009

Methods	Randomized controlled trial
Participants	Setting: University Hospital in Germany. Surgical ICU. Staffing ratios not stated Participants: 60 patients, (intervention 30, control 30). Conditions: abdominal, vascular, thoracic & trauma/orthopaedic surgery Inclusion: 18-80 years, mechanically ventilated via endotracheal tube or tracheostomy for at least 24-hours; breathing spontaneously; Ramsay sedation score $\leq$3; paO_2 >75cm H_2O or SaO_2 >90% at FiO_2 $\leq$0.5; 18-80 years; body weight 35kg-200kg. Exclusion: PEEP >10cm H_2O; haemodynamic instability with demand for catecholamines; rectal temperature >39^{o}C; haemoglobin <7g/dl; pH>7.2.
Interventions	Intervention: computerized automated weaning of CPAP/ASB mode (SmartCare ^{TM}/PS) Control: physician-directed weaning using no strict protocol, but PSV should be gradually reduced in single steps of no more than 15cm H_2O. Extubation criteria: respiratory rate, 30/minute; paO_2 >75cm H_2O or SaO_2 >90%; sufficient airway protection; haemodynamic stability.
Outcomes	1. Duration of ventilator weaning in days (time from switching controlled to assisted breathing (CPAP/ASB mode) until extubation or disconnection (if tracheostomy) 2. Total duration of MV until successful extubation 3. ICU LOS 4. Reintubation within 48-hours 5. Physician workload (quantity of PSV, FiO_2 and PEEP settings/hour) 6. Nursing workload (frequency of alarm "clean CO_2 cuvette"/hour) 7. ICU and hospital mortality
Notes	Local ethics committee approval; signed informed consent from patients or relatives

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization list generated using RITA version 1.13a. Stratified randomization with age and duration of MV prior to weaning
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, staff and research personnel were unblinded to the intervention. On contact, authors stated that "outcome assessors were independent from those managing

Stahl 2009 (*Continued*)

		patient care"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All a priori outcomes reported. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Appears to be free of other sources of bias.
Other bias	Unclear risk	Sample size calculation stated (based on 80% power to detect a difference of 2-days in weaning time, α 0.05, 54 patients each group). Unplanned interim analysis was undertaken because of low recruitment after 1-year: sample size and significance levels were recalculated (N = 60 patients) and after the 60th patient the trial was stopped for futility

Strickland 1993

Methods	Randomized controlled trial
Participants	Setting: USA, Medical ICU. Hospital description and staffing ratios not stated Participants: 15 adult patients (intervention 9, control 6). Conditions: COPD/asthma; septic shock; ARDS; pulmonary oedema Inclusion: mechanically ventilated; judged ready to wean by physicians and meeting prespecified inclusion criteria Exclusion: post-operative patients < 3-days.
Interventions	Intervention: protocol delivered by a computer-controlled weaning system (Supersport model 2, Zenith Data Systems) consisting of stepwise reductions in SIMV and PSV responsive to tidal volume & respiratory rate sampling (computer directed algorithm) Control: weaning with SIMV and PS reduction as judged appropriate by the patient's physician
Outcomes	1. Time spent with RR <8 or >30 2. Time spent with tidal volume <5ml/kg 3. No. of arterial blood gases drawn during weaning 4. Weaning duration 5. MV prior to weaning
Notes	Study period and data collection were limited to 48-hours because only one computer system was available for the study Study approved by hospital Institutional Review Board and informed consent required

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.

Strickland 1993 (*Continued*)

Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors were independent from the individuals administering/supervising the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Low risk	Appears to be free of other sources of bias. No sample size calculation stated

ARDS - acute respiratory distress syndrome; ASB - assisted spontaneous breathing; CPAP - continuous positive airway pressure; CHF - congestive heart failure; COPD - chronic obstructive pulmonary disease; GI - gastro-intestinal; ICU - intensive care unit; IMV - intermittent mandatory ventilation; ITT - intention to treat; MD - medical doctor; MSOF - multi-system organ failure; MV - mechanical ventilation; PC - personal computer; PEEP - positive end expiratory pressure; PS - pressure support; PSV - pressure support ventilation; RN - registered nurse; RR - respiratory rate; RT - respiratory therapist; SBT- spontaneous breathing trial; SD - standard deviation; VAP - ventilator associated pneumonia.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beale 2008	Compared an automated protocol with protocol guided weaning. The comparator did not fulfil our inclusion criteria
Butler 2007	This was a cluster randomized controlled trial comparing an evidence based protocol with standard practice (no guidelines). The study was stopped due to recruitment problems and we were unable to obtain sufficient data to include it in the review
Donglemans 2009	Intervention group was weaned using a computer protocol and compared with a control group where weaning was undertaken using standardized guidelines. Control group did not meet the review inclusion criteria (i.e. was not 'non-protocolized' according to our definition)
East 1999	The authors evaluated automated (computerized) protocolized weaning in a population of ARDS patients using a cluster randomized controlled trial. From the papers, we were unable to identify the comparator or the weaning outcomes and we were unable to contact the authors to obtain further information
Lellouche 2006	Intervention group was weaned using a computer protocol and compared with a control group where weaning was undertaken using standardized guidelines. Control group did not meet the review inclusion criteria (i.e. was not 'non-protocolized' according to our definition)

(*Continued)*

McKinley 2001	The authors evaluated automated (computerized) protocolized weaning in a population of ARDS patients using a cluster randomized controlled trial. From the papers, we were unable to identify the comparator or the weaning outcomes and we were unable to contact the authors to obtain further information
Papirov 2008	Ongoing RCT comparing a computer-driven protocol with physician-directed protocol. Control group weaning is not 'non-protocolized' according to our definition
Scholz 2008	Compared an automated protocol with a standard weaning protocol. The comparator did not fulfil our inclusion criteria
Taniguchi 2009	Intervention group was weaned using a computer protocol and compared with a control group where weaning was undertaken using standardized guidelines. Control group did not meet the review inclusion criteria (i.e. was not 'non-protocolized' according to our definition)

RCT - randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Reardon 2009

Trial name or title	Clinical trial of a computer-driven weaning system for patients requiring mechanical ventilation
Methods	Randomized controlled trial
Participants	18-years and older Mechanically ventilated via endotracheal tube Requiring mechanical ventilation for > 48-hours Admitted to Medical ICU Meets pre-specified weaning criteria
Interventions	Intervention: computer-driven weaning program - Drager Evita Smartcare System Control: usual care weaning
Outcomes	1. Duration of weaning 2. Duration of ICU stay 3. Duration of mechanical ventilation 4. Duration of hospitalization 5. Mortality 6. Sedation requirements 7. No. of SBTs prior to extubation 8. Complications (mortality during weaning; VAP; self-extubation; re-intubation rate)
Starting date	January 2008

Reardon 2009 (*Continued*)

Contact information	Christine C Reardon Boston University Medical Center Boston, Massachusetts, USA Email: creardon@bu.edu; Allan.Walkey@bmc.org
Notes	Estimated completion date November 2009

ICU - intensive care unit; SBT - spontaneous breathing trial; VAP - ventilator associated pneumonia ;

DATA AND ANALYSES

Comparison 1. Primary analysis: protocolized versus non-protocolized weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total duration of MV by type of unit	10	1873	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.50, -0.09]
1.1 Mixed ICUs	4	830	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.54, 0.09]
1.2 Neuro ICUs	2	418	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.20, 0.18]
1.3 Surgical ICUs	2	101	Mean Difference (IV, Random, 95% CI)	-0.66 [-1.25, -0.06]
1.4 Medical ICUs	2	524	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.81, 0.11]
2 Total duration of MV by type of approach	10	1873	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.50, -0.09]
2.1 professional-led	8	1719	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.43, -0.06]
2.2 computer-driven	2	154	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.42, 0.42]
3 Mortality	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Hospital mortality	6	1368	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.86, 1.41]
3.2 ICU mortality	4	508	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.48, 2.02]
4 Reintubation	8	1314	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.40, 1.42]
5 Tracheostomy	6	1191	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.45, 1.22]
6 Weaning duration	6	834	Mean Difference (IV, Random, 95% CI)	-1.52 [-2.66, -0.37]
7 ICU length of stay	8	1256	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.21, -0.02]
8 l Hospital length of stay	4	859	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.11, 0.10]
9 ICU costs	2	400	Mean Difference (IV, Random, 95% CI)	3.37 [-15.02, 21.76]
10 Hospital costs	3	757	Mean Difference (IV, Random, 95% CI)	-0.59 [-4.67, 3.49]

Comparison 2. Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total duration of MV	8	1613	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.57, -0.12]
2 Weaning duration	5	499	Mean Difference (IV, Random, 95% CI)	-1.64 [-3.18, -0.10]

Comparison 3. Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total duration of MV	10	1873	Mean Difference (IV, Random, 95% CI)	-19.50 [-35.91, -3.10]
2 Weaning duration	6	706	Mean Difference (IV, Random, 95% CI)	-39.41 [-68.74, -10.09]
3 ICU length of stay	8	1256	Mean Difference (IV, Fixed, 95% CI)	-18.32 [-30.40, -6.25]
4 Hospital length of stay	4	859	Mean Difference (IV, Fixed, 95% CI)	-1.32 [-3.10, 0.46]

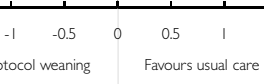
Analysis 1.1. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 1 Total duration of MV by type of unit.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 1 Total duration of MV by type of unit

Study or subgroup	Experimental N	Experimental Mean(SD)[log hours]	Control N	Control Mean(SD)[log hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Mixed ICUs							
Kollef 1997	179	3.33 (1.2)	178	3.56 (0.96)		12.1 %	-0.23 [-0.46, 0.00]
Marelich 2000	166	4.22 (1.2)	169	4.82 (1.36)		11.3 %	-0.60 [-0.87, -0.33]
Piotto 2008	18	4.27 (1.39)	18	3.81 (1.44)		3.7 %	0.46 [-0.46, 1.38]
Rose 2008	51	4.793 (0.752)	51	4.83 (0.863)		10.7 %	-0.04 [-0.35, 0.28]
Subtotal (95% CI)	**414**		**416**			**37.8 %**	**-0.23 [-0.54, 0.09]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 10.20$, df = 3 (P = 0.02); $I^2 = 71\%$							
Test for overall effect: Z = 1.42 (P = 0.16)							
2 Neuro ICUs							
Namen 2001	49	4.97 (0.75)	51	4.97 (1.4)		8.7 %	0.0 [-0.44, 0.44]
Navalesi 2008	165	4.328 (0.92)	153	4.34 (0.96)		12.4 %	-0.01 [-0.22, 0.20]
Subtotal (95% CI)	**214**		**204**			**21.1 %**	**-0.01 [-0.20, 0.18]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.09 (P = 0.93)							
3 Surgical ICUs							
Simeone 2002	24	1.72 (0.54)	25	2.08 (0.39)		11.5 %	-0.36 [-0.62, -0.10]



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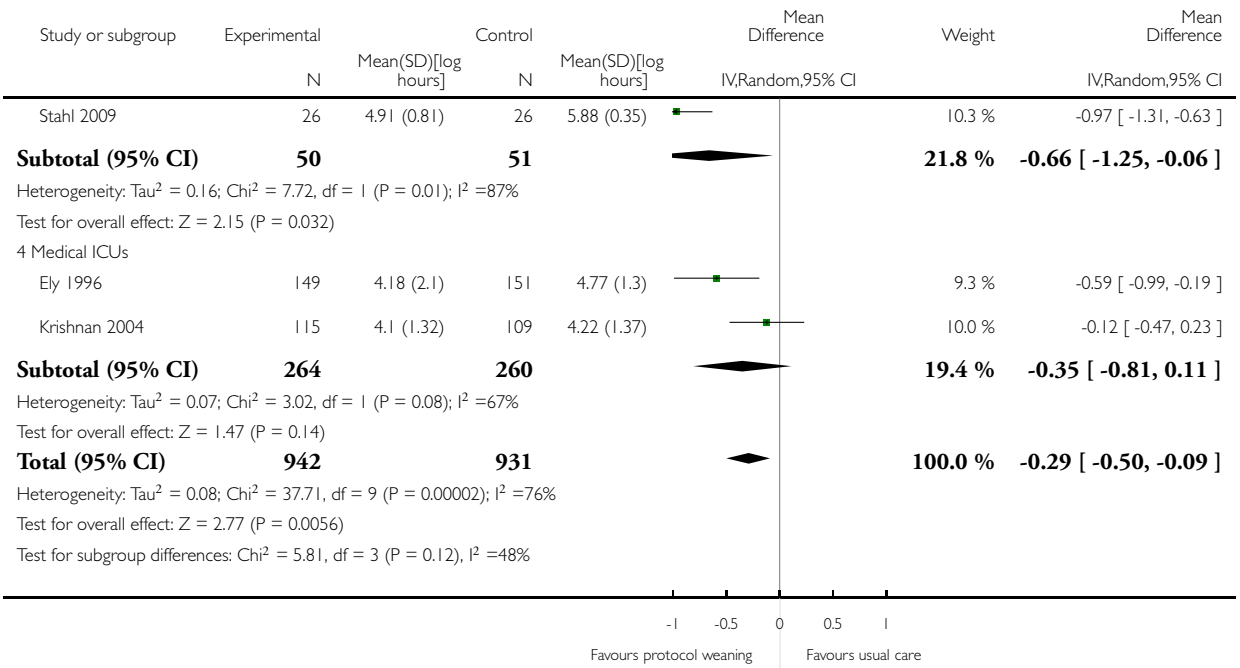
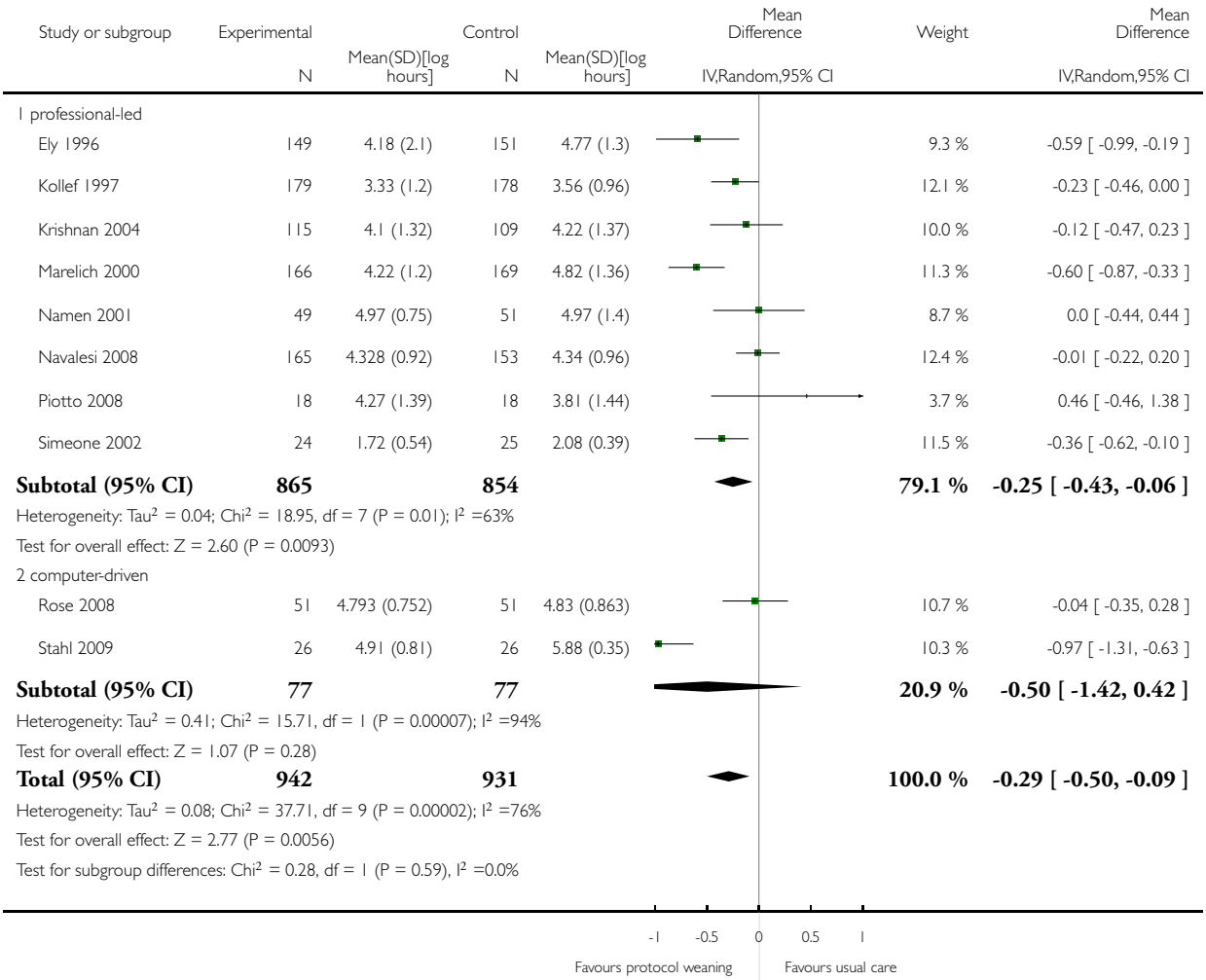


Analysis 1.2. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 2 Total duration of MV by type of approach.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 2 Total duration of MV by type of approach



Analysis 1.3. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 3 Mortality.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 3 Mortality

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Hospital mortality					
Ely 1996	56/149	60/151		31.7 %	0.91 [0.57, 1.45]
Kollef 1997	40/179	42/178		27.9 %	0.93 [0.57, 1.53]
Krishnan 2004	56/115	48/109		21.5 %	1.21 [0.71, 2.04]
Marelich 2000	17/166	10/169		7.6 %	1.81 [0.81, 4.09]
Namen 2001	20/49	16/51		7.9 %	1.51 [0.66, 3.43]
Stahl 2009	5/26	5/26		3.4 %	1.00 [0.25, 3.97]
Subtotal (95% CI)	**684**	**684**		**100.0 %**	**1.10 [0.86, 1.41]**
Total events: 194 (Experimental), 181 (Control)					
Heterogeneity: Chi^2 = 3.21, df = 5 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 0.75 (P = 0.46)					
2 ICU mortality					
Navalesi 2008	2/165	6/153		41.3 %	0.30 [0.06, 1.51]
Piotto 2008	7/18	10/18		41.0 %	0.51 [0.13, 1.92]
Rose 2008	7/51	1/51		5.8 %	7.95 [0.94, 67.21]
Stahl 2009	3/26	2/26		11.9 %	1.57 [0.24, 10.24]
Subtotal (95% CI)	**260**	**248**		**100.0 %**	**0.98 [0.48, 2.02]**
Total events: 19 (Experimental), 19 (Control)					
Heterogeneity: Chi^2 = 6.93, df = 3 (P = 0.07); I^2 =57%					
Test for overall effect: Z = 0.06 (P = 0.96)					

Analysis 1.4. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 4 Reintubation.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 4 Reintubation

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Ely 1996	5/149	12/151		14.1 %	0.40 [0.14, 1.17]
Kollef 1997	23/179	18/178		18.9 %	1.31 [0.68, 2.52]
Namen 2001	10/49	6/51		13.8 %	1.92 [0.64, 5.77]
Navalesi 2008	9/165	18/153		16.8 %	0.43 [0.19, 0.99]
Piotto 2008	2/18	11/18		8.4 %	0.08 [0.01, 0.46]
Rose 2008	5/51	6/51		12.2 %	0.82 [0.23, 2.86]
Simeone 2002	1/24	0/25		3.2 %	3.26 [0.13, 83.90]
Stahl 2009	8/26	6/26		12.4 %	1.48 [0.43, 5.10]
Total (95% CI)	**661**	**653**		**100.0 %**	**0.76 [0.40, 1.42]**

Total events: 63 (Experimental), 77 (Control)

Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 16.70$, df = 7 (P = 0.02); $I^2 = 58\%$

Test for overall effect: Z = 0.87 (P = 0.39)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 5 Tracheostomy.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 5 Tracheostomy

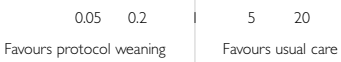
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Ely 1996	13/149	22/151		22.9 %	0.56 [0.27, 1.16]
Marelich 2000	13/166	21/169		22.9 %	0.60 [0.29, 1.24]
Namen 2001	14/49	15/51		19.1 %	0.96 [0.40, 2.28]
Navalesi 2008	5/165	11/153		14.5 %	0.40 [0.14, 1.19]
Piotto 2008	8/18	2/18		7.1 %	6.40 [1.12, 36.44]
Rose 2008	6/51	8/51		13.6 %	0.72 [0.23, 2.24]
Total (95% CI)	**598**	**593**		**100.0 %**	**0.74 [0.45, 1.22]**

Total events: 59 (Experimental), 79 (Control)

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 8.29$, df = 5 (P = 0.14); $I^2 = 40\%$

Test for overall effect: Z = 1.18 (P = 0.24)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 6 Weaning duration.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 6 Weaning duration

Study or subgroup	Experimental N	Mean(SD)[log hours]	Control N	Mean(SD)[log hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ely 1996	149	0.29 (3.84)	151	3.64 (2.56)		16.4 %	-3.35 [-4.09, -2.61]
Marelich 2000	166	3.64 (1.41)	169	4.57 (1.44)		17.4 %	-0.93 [-1.24, -0.62]
Piotto 2008	18	0.72 (0.2)	18	3.92 (0.8)		17.3 %	-3.20 [-3.58, -2.82]
Rose 2008	51	3.405 (1.464)	51	3.4 (1.869)		16.7 %	0.00 [-0.65, 0.65]
Stahl 2009	26	2.73 (2.26)	26	4.02 (1.9)		15.0 %	-1.29 [-2.42, -0.16]
Strickland 1993	7	2.88 (0.31)	2	3.22 (0.22)		17.3 %	-0.34 [-0.72, 0.04]
Total (95% CI)	**417**		**417**			**100.0 %**	**-1.52 [-2.66, -0.37]**

Heterogeneity: $Tau^2 = 1.94$; $Chi^2 = 169.00$, df = 5 ($P<0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 2.59 (P = 0.0095)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 7 ICU length of stay.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 7 ICU length of stay

Study or subgroup	Experimental N	Mean(SD)[log hours]	Control N	Mean(SD)[log hours]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ely 1996	149	3.72 (2.4)	151	3.78 (2.1)		3.6 %	-0.06 [-0.57, 0.45]
Krishnan 2004	154	4.74 (1.01)	145	4.98 (0.95)		19.2 %	-0.24 [-0.46, -0.02]
Namen 2001	49	5.89 (0.42)	51	5.82 (0.79)		15.6 %	0.07 [-0.18, 0.32]
Navalesi 2008	165	4.93 (0.8)	153	5.04 (0.79)		31.0 %	-0.11 [-0.28, 0.06]
Piotto 2008	18	6.06 (0.72)	18	6.15 (0.66)		4.7 %	-0.09 [-0.54, 0.36]
Rose 2008	51	5.09 (0.67)	51	5.18 (0.79)		11.7 %	-0.09 [-0.37, 0.19]
Simeone 2002	24	3.24 (0.51)	25	3.61 (0.66)		8.7 %	-0.37 [-0.70, -0.04]
Stahl 2009	26	6.26 (0.78)	26	6.16 (0.74)		5.5 %	0.10 [-0.31, 0.51]
Total (95% CI)	**636**		**620**			**100.0 %**	**-0.11 [-0.21, -0.02]**

Heterogeneity: Chi^2 = 6.81, df = 7 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 2.27 (P = 0.023)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 8 1 Hospital length of stay.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 8 1 Hospital length of stay

Study or subgroup	Experimental N	Mean(SD)[log days]	Control N	Mean(SD)[log days]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ely 1996	149	5.82 (0.79)	151	5.92 (1.2)		20.4 %	-0.10 [-0.33, 0.13]
Kollef 1997	179	5.58 (0.66)	178	5.58 (0.72)		52.5 %	0.0 [-0.14, 0.14]
Namen 2001	49	6.87 (0.62)	51	6.64 (0.9)		11.8 %	0.23 [-0.07, 0.53]
Rose 2008	51	2.89 (0.68)	51	2.98 (0.69)		15.2 %	-0.09 [-0.36, 0.18]
Total (95% CI)	**428**		**431**			**100.0 %**	**-0.01 [-0.11, 0.10]**

Heterogeneity: $Chi^2 = 3.38$, df = 3 (P = 0.34); $I^2 = 11\%$

Test for overall effect: Z = 0.13 (P = 0.90)

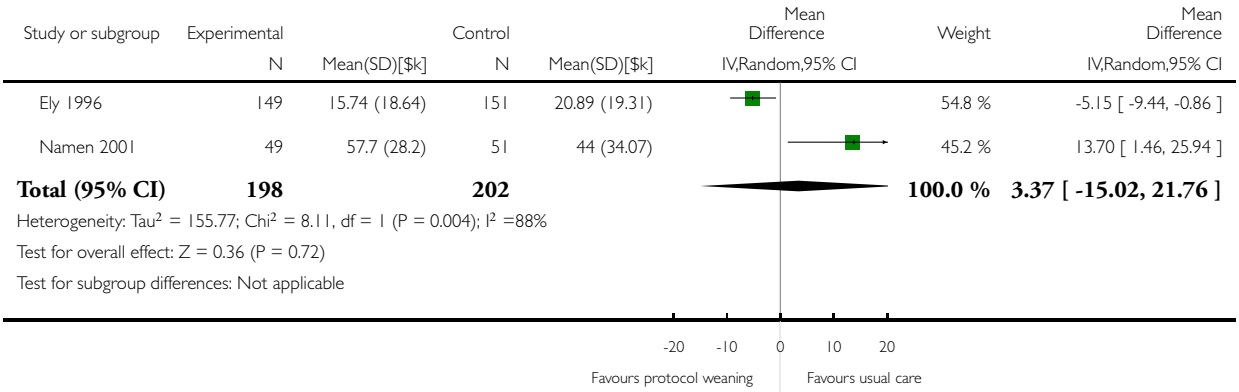
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 9 ICU costs.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 9 ICU costs

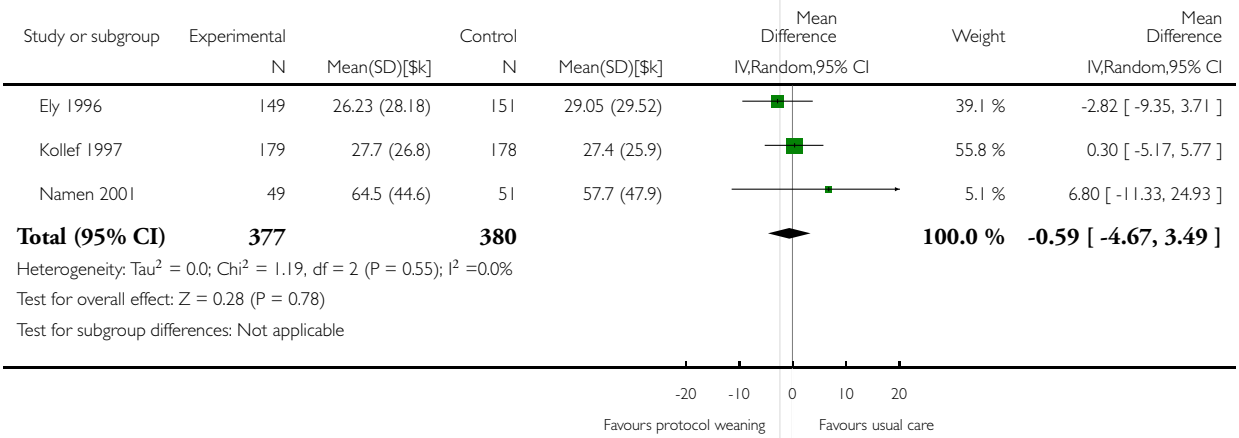


Analysis 1.10. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 10 Hospital costs.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 10 Hospital costs



Analysis 2.1. Comparison 2 Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies, Outcome 1 Total duration of MV.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 2 Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies

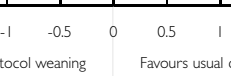
Outcome: 1 Total duration of MV

Study or subgroup	Experimental N	Mean(SD)[log hours]	Control N	Mean(SD)[log hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ely 1996	149	4.18 (2.1)	151	4.77 (1.3)		10.9 %	-0.59 [-0.99, -0.19]
Kollef 1997	179	3.33 (1.2)	178	3.56 (0.96)		14.0 %	-0.23 [-0.46, 0.00]
Marelich 2000	166	4.22 (1.2)	169	4.82 (1.36)		13.1 %	-0.60 [-0.87, -0.33]
Namen 2001	49	4.97 (0.75)	51	4.97 (1.4)		10.1 %	0.0 [-0.44, 0.44]
Navalesi 2008	165	4.328 (0.92)	153	4.34 (0.96)		14.3 %	-0.01 [-0.22, 0.20]
Rose 2008	51	4.793 (0.752)	51	4.83 (0.863)		12.4 %	-0.04 [-0.35, 0.28]
Simeone 2002	24	1.72 (0.54)	25	2.08 (0.39)		13.3 %	-0.36 [-0.62, -0.10]
Stahl 2009	26	4.91 (0.81)	26	5.88 (0.35)		11.9 %	-0.97 [-1.31, -0.63]
Total (95% CI)	**809**		**804**			**100.0 %**	**-0.34 [-0.57, -0.12]**

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 34.28$, df = 7 (P = 0.00002); $I^2 = 80\%$

Test for overall effect: Z = 2.97 (P = 0.0030)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies, Outcome 2 Weaning duration.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 2 Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies

Outcome: 2 Weaning duration

Study or subgroup	Experimental N	Mean(SD)[log hours]	Control N	Mean(SD)[log hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ely 1996	149	0.29 (3.84)	151	3.64 (2.56)		19.9 %	-3.35 [-4.09, -2.61]
Marelich 2000	18	0.72 (0.2)	18	3.92 (0.8)		20.6 %	-3.20 [-3.58, -2.82]
Rose 2008	51	3.405 (1.464)	51	3.4 (1.869)		20.1 %	0.00 [-0.65, 0.65]
Stahl 2009	26	2.73 (2.26)	26	4.02 (1.9)		18.8 %	-1.29 [-2.42, -0.16]
Strickland 1993	7	2.88 (0.31)	2	3.22 (0.22)		20.6 %	-0.34 [-0.72, 0.04]
Total (95% CI)	**251**		**248**			**100.0 %**	**-1.64 [-3.18, -0.10]**

Heterogeneity: $Tau^2 = 2.97$; $Chi^2 = 154.11$, df = 4 ($P<0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 2.08 (P = 0.037)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data, Outcome 1 Total duration of MV.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome: 1 Total duration of MV

Study or subgroup	Experimental N	Mean(SD)[hours]	Control N	Mean(SD)[hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ely 1996	149	151.2 (175.2)	151	211.2 (261.6)		7.5 %	-60.00 [-110.32, -9.68]
Kollef 1997	179	69.4 (123.7)	178	102 (169.1)		13.3 %	-32.60 [-63.35, -1.85]
Krishnan 2004	115	60.4 (103)	109	68 (105.3)		14.8 %	-7.60 [-34.90, 19.70]
Marelich 2000	166	68 (97)	169	124 (207)		11.9 %	-56.00 [-90.52, -21.48]
Namen 2001	49	144 (124.45)	51	144 (195.56)		5.2 %	0.0 [-63.99, 63.99]
Navalesi 2008	165	120 (134.4)	153	120 (120)		14.5 %	0.0 [-27.97, 27.97]
Piotto 2008	18	189.25 (463.55)	18	127.48 (337.37)		0.4 %	61.77 [-203.09, 326.63]
Rose 2008	51	119 (174.89)	51	129 (197.07)		4.3 %	-10.00 [-82.31, 62.31]
Simeone 2002	24	6.54 (3.78)	25	8.58 (3.45)		24.8 %	-2.04 [-4.07, -0.01]
Stahl 2009	26	135.6 (122.1)	26	199.44 (172.3)		3.5 %	-63.84 [-145.01, 17.33]
Total (95% CI)	**942**		**931**			**100.0 %**	**-19.50 [-35.91, -3.10]**

Heterogeneity: $Tau^2 = 281.11$; $Chi^2 = 20.75$, df = 9 (P = 0.01); $I^2 = 57\%$

Test for overall effect: Z = 2.33 (P = 0.020)

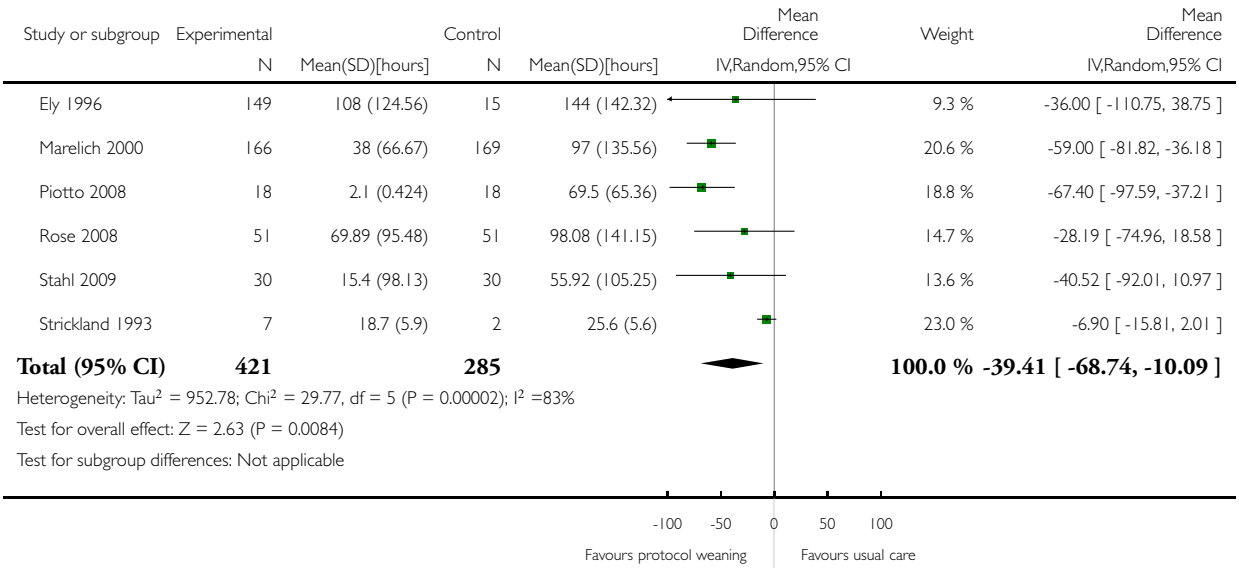
Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data, Outcome 2 Weaning duration.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome: 2 Weaning duration



Analysis 3.3. Comparison 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data, Outcome 3 ICU length of stay.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome: 3 ICU length of stay

Study or subgroup	Experimental N	Mean(SD)[hours]	Control N	Mean(SD)[hours]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ely 1996	149	192 (248.88)	151	216 (10.9)		9.1 %	-24.00 [-64.00, 16.00]
Krishnan 2004	154	115 (209.37)	145	146 (155.56)		8.4 %	-31.00 [-72.65, 10.65]
Namen 2001	49	360 (160)	51	336 (266.67)		2.0 %	24.00 [-61.81, 109.81]
Navalesi 2008	165	194.4 (172.8)	153	211.2 (175.2)		9.9 %	-16.80 [-55.09, 21.49]
Piotto 2008	18	554.4 (458.2)	18	564 (373.4)		0.2 %	-9.60 [-282.66, 263.46]
Rose 2008 (1)	51	205.37 (157.17)	51	243.73 (218.57)		2.7 %	-38.36 [-112.25, 35.53]
Simeone 2002	24	29 (15.8)	25	46.1 (33.9)		67.3 %	-17.10 [-31.82, -2.38]
Stahl 2009	26	522.72 (352.2)	26	471.6 (338.86)		0.4 %	51.12 [-136.74, 238.98]
Total (95% CI)	**636**		**620**			**100.0 %**	**-18.32 [-30.40, -6.25]**

Heterogeneity: Chi^2 = 2.21, df = 7 (P = 0.95); I^2 =0.0%

Test for overall effect: Z = 2.98 (P = 0.0029)

Test for subgroup differences: Not applicable

(1) Hours

Analysis 3.4. Comparison 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data, Outcome 4 Hospital length of stay.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome: 4 Hospital length of stay

Study or subgroup	Experimental N	Mean(SD)[days]	Control N	Mean(SD)[days]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ely 1996	149	14 (12.59)	151	15.5 (17.78)		26.1 %	-1.50 [-4.98, 1.98]
Kollef 1997	179	12.7 (9.4)	178	14.2 (11.7)		65.2 %	-1.50 [-3.70, 0.70]
Namen 2001	49	40 (31)	51	32 (35)		1.9 %	8.00 [-4.95, 20.95]
Rose 2008	51	22.98 (18.8)	51	24.45 (16.07)		6.9 %	-1.47 [-8.26, 5.32]
Total (95% CI)	**428**		**431**			**100.0 %**	**-1.32 [-3.10, 0.46]**

Heterogeneity: Chi^2 = 2.03, df = 3 (P = 0.57); I^2 =0.0%

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Readiness to wean criteria

Study	Assessment Frequency	Oxygenation	Other respiratory factors	Cardiovascular	Neurological	Inflammatory response	Medication	Other
Ely 1996	Daily screen	PaO_2/FiO_2 > 200	PEEP </= 5 f/VT </= 105				No vasopressors or sedation	Adequate cough.
Kollef 1997	Protocol entry criteria	PaO_2/FiO_2 > 200	PEEP </= 5 RR </= 35 b/min	HR < 140b/min	Awake & orientated		No vasoactive or inotropic agents	
Krishnan 2004	Daily screen	SpO_2 >/= 92% FiO_2 </= 0.5	PEEP </=5	Stable CAD HR < 140b/min	No raised ICP		No paralytics	Cough & gag reflex present.

Table 1. Readiness to wean criteria (*Continued*)

								Responsive to stimuli.
Marelich 2000	x 2 daily screen	PaO_2/FiO^2 >/= 200		MAP >/= 60mmHg	GCS >/= 10 or tracheostomy		No vasopressors Dopamine </= 5ug/kg/min	Adequate cough not limited by pain.
Namen 2001	Daily screen	PaO_2/FiO_2 > 200	PEEP </= 5 f/VT </= 105				No vasopressors or sedation	Adequate cough.
Navalesi 2008	Daily screen	PaO_2/FiO_2 > 200 FiO_2 </= 0.4 pH >/= 7.35 $PaCO_2$ </= 50mmHg	PEEP </= 5	HR </= 125 b/min SBP >/= 90mmHg	GCS >/= 8	T < 38.5°C	No vasopressors. Dopamine </= 5ug/kg/min	Adequate cough. Suctioning < 2/hr. Normal Na blood values.
Piotto 2008	Daily screen	PaO_2/FiO_2 150-300 FiO_2 </= 0.4 PaO_2 >/= 60 Hb = 8-10g/l		MAP >/= 60mmHg HR </= 140b/min	Awake GCS >/= 9	T < 37.8°C	Minimum sedation No or low vasopressors	Cause of MV resolved. Effective cough. Metabolic stability. No hydro electrolyte disorders.
Rose 2008	Inclusion criteria	PaO_2/FiO_2 > 150 or SaO_2 >/= 90% on FiO_2 0.5	PEEP </= 8 Plateau pressure </= 30cmH_2O. Successful 30-min SBT using PS 20cmH_2O to achieve VT > 200ml.	Haemodynamically stable	GCS > 4	T 36-39°C		No surgery anticipated. MV > 24 hr.

Table 1. Readiness to wean criteria (*Continued*)

Simeone 2002	Inclusion criteria	PaO2/FiO_2 >/= 200 FiO_2 < 0.5 pH 7.3-7.5 PaO_2 30-50mmHg SaO_2 > 90% Hb > 8mg/dl Pulse oximeter oxygenation stable. Cardiopulmonary bypass time < 150 min.	PEEP < 4 RR < 35 b/min (2min after MV discontinuation) Dynamic compliance > 22ml/cmH_2O. Compliance statica >33ml/cmH_2O. Vital capacity >10ml/kg. MIP >/= -15cmH_2O	Haemodynamically stable	Awake & conscious	T>35< 38 ^oC		Urine output > 100ml/hr. Normal CXR.
Stahl 2009	Inclusion criteria	FiO_2 </= 0.5 PaO_2 > 75cm H_2O or SaO_2 > 90% pH </= 7.2 Hb >/= 7g/dl	PEEP </= 10	Haemodynamically stable			Dopamine </= 5ug/kg/min	MV > 24 hr. Breathing spontaneously. Ramsey sedation score =/< 3.
Strickland 1993	Inclusion criteria	FiO_2 </= 0.4 pH >/= 7.3 </= 7.5 PCO_2 >/= 30 </= 50 SaO_2 >/= 90% on SIMV rate 6-10 PS 20cmH_2O	NIF </= -20cmH_2O FVC >/= 10ml/kg TV 10-15 ml/kg	Haemodynamically stable		T </=37^oC		Judged ready to wean by physician. Feeding - parenteral or tube. Stable renal function. Normal electrolytes.

CAD = coronary artery diease; CXR = chest X-ray; GCS = Glasgow Coma Scale; FVC = forced vital capacity; Hb = haemoglobin; HR - heart rate; MAP = mean arterial pressure; MIP = maximal inspiratory pressure; MV = mechanical ventilation; NIF = negative inspiratory force; PEEP = positive end expiratory pressure; PS = pressure support; RR = respiratory rate; SBP = systolic blood pressure; SIMV = synchronized intermittent mechanical ventilation; T = temperature; TV = tidal volume; VT = tidal volume.

Table 2. Weaning protocol differences

Study	Screen	Weaning method	Extubation criteria
Ely 1996	Daily	SBT 2-hour on CPAP 5cmH $_2$ 0	Notify MD
Kollef 1997		a) SBT 30 to 60 min on CPAP 5cmH $_2$ 0, PS 6cmH $_2$ 0 b) PS stepwise reduction to 6cmH $_2$ 0 c) IMV stepwise reduction to 0 breaths/min, on PEEP 5cmH $_2$ 0 & PS 6cmH $_2$ 0 for 30 to 60 min	a) Yes b) Yes c) Yes
Krishnan 2004	Daily	SBT 1-hour onCPAP 5cmH $_2$ 0	Notify MD
Marelich 2000	Twice daily	a) < 72-hour admissions: SBT 30 min on PS </= 8cmH $_2$ 0 & PEEP </= 8cmH $_2$ 0 b) > 72-hour admissions: PEEP, IMV & PS stepwise reductions to achieve FiO $_2$ 0.5, PEEP </= 8cmH $_2$ 0, IMV </= 6 breaths/min, PS </= 8cmH $_2$ 0 then SBT as above.	a) Notify MD b) Notify MD
Namen 2001	Daily	SBT 2-hour on CPAP 5cmH $_2$ 0	Notify MD
Navalesi 2008	Daily	SBT 1-hour on CPAP 2 to 3 cmH $_2$ 0, FiO $_2$ 0.4	Yes
Piotto 2008	Daily	SBT 2-hour on PS 7cmH $_2$ 0, PEEP 5cmH $_2$ 0, FiO $_2$ 0.4, RR 1breath/min	Yes
Rose 2008		Computer automated SmartCare^{TM}/PS with stepwise reductions to PS 7cmH $_2$ 0 & PEEP 5cmH $_2$ 0	No
Simeone 2002		SIMV & PS stepwise reductions to SIMV 0 breath/min & PS 4cmH $_2$ 0	Yes
Stahl 2009		Computer automated SmartCare^{TM}/PS stepwise reductions to PS	Yes

Table 2. Weaning protocol differences (*Continued*)

Strickland 1993		Computer automated Supersport model 2 stepwise reductions in SIMV & PS to RR 2 breaths/min & PS 5cmH $_2$ 0	

CPAP = continuous positive airway pressure; IMV = intermittent mechanical ventilation; PEEP = positive end expiratory pressurePS = pressure support; SBT = spontaneous breathing trial; SIMV =synchronized intermittent mechanical ventilation; RR = respiratory rate.

APPENDICES

Appendix 1. Ovid MEDLINE(R) in-process and other non-indexed citations and Ovid MEDLINE(R) (1950 to 3rd week January 2010)

#1 exp Ventilator Weaning/
#2 mechanical ventilat$ weaning.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#3 mechanical ventilation.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#4 (protocol$ adj weaning).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#5 (ventilat$ adj weaning).mp. [mpP=title, original title, abstract, name of substance word, subject heading word]
#6 exp Ventilators, Mechanical/
#7 exp Ventilators, Negative-Pressure/
#8 (mechanical adj ventilat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#9 (mechanical adj weaning).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#10 ventilat$.ab,ti.
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 protocol$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#13 exp Clinical Protocols/
#14 exp Patient Care Management/
#15 Practice Guidelines/
#16 #12 or #13 or #14 or #15
#17 #11 and #16
#18 clinical trial.pt.
#19 randomized.ab.
#20 placebo.ab.
#21exp Clinical Trials/
#22 randomly.ab.
#23 trial.ti.
#24 #18 or #19 or #20 or #21 or #22 or #23
#25 Animals/
#26 Humans/
#27 #25 not (#25 and #26)
#28 #24 not #27
#29 #17 and #28

Appendix 2. EMBASE (1988 to week 4 January 2010)

#1 exp Ventilator Weaning/
#2 mechanical ventilat$ weaning.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#3 mechanical ventilation.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#4 (protocol$ adj weaning).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#5 (ventilat$ adj weaning).mp. [mpP=title, original title, abstract, name of substance word, subject heading word]
#6 exp Ventilators, Mechanical/
#7 exp Ventilators, Negative-Pressure/
#8 (mechanical adj ventilat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#9 (mechanical adj weaning).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#10 ventilat$.ab,ti.
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 protocol$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
#13 exp Clinical Protocols/
#14 exp Patient Care Management/
#15 Practice Guidelines/
#16 #12 or #13 or #14 or #15
#17 #11 and #16
#18 clinical trial.pt.
#19 randomized.ab.
#20 placebo.ab.
#21exp Clinical Trials/
#22 randomly.ab.
#23 trial.ti.
#24 #18 or #19 or #20 or #21 or #22 or #23
#25 Animals/
#26 Humans/
#27 #25 not (#25 and #26)
#28 #24 not #27
#29 #17 and #28

Appendix 3. LILACS (via BIREME interface) (1982 to January 2010)

1 “WEANING” or “MECHANICAL VENTILATION” or “VENTILATOR“ or ”NEGATIVE-PRESSURE“ [Words] or ”ventilat* weaning“ or ”mechanical ventilator*“ or ”destetar mecánico“ or ”desmamar mecânico“ [Words]

Appendix 4. CINAHL Plus EBSCO host (1937 to 2010)

#1 (MM ”Ventilators, Mechanical“) or (MM ”Ventilator Weaning“) or (MH”Respiration, artificial+”)
#2 (“mechanical ventilat$ weaning”) or (“MH Ventilator Weaning”) or (MH “Mechanical Ventilatory Weaning (Iowa NIC)”) or (MH “Ventilatory Weaning Impairment (Saba CCC)”)
#3 “mechanical ventilation”
#4 “weaning protocol”
#5 #1 or #2 or #3 or #4
#6 (“protocol$”) or (MM “Nursing Protocols+”)
#7 (MM “Practice Guidelines”)
#8 #6 or #7
#9 #5 and #8
#10 (MM “Clinical Trials+”)
#11 (MH “Random Assignment”)
#12 “randomly”
#13 “trial”
#14 #10 or #11 or #12 or #13

#15 #9 and #14

Appendix 5. CENTRAL (*The Cochrane Library* 2010 Issue 1)

#1 MeSH descriptor Ventilator Weaning explode all trees
#2 mechanical ventilat* weaning
#3 protocol* near weaning
#4 ventilat* near weaning
#5 MeSH descriptor Ventilators, Mechanical explode all trees
#6 MeSH descriptor Ventilators, Negative-Pressure explode all trees
#7 (mechanical ventilat*):ab
#8 mechanical near weaning
#9 ventilat*:ti
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 protocol*:ti,ab
#12 MeSH descriptor Clinical Protocols explode all trees
#13 MeSH descriptor Patient Care Management explode all trees
#14 MeSH descriptor Practice Guidelines explode all trees
#15 (#11 OR #12 OR #13 OR #14)
#16 (#10 AND #15)

Appendix 6. ISI Web of Science with Conference Proceedings (1970 to January 2010)

#1 TS=mechanical ventilat*
#3 TS=(ventilat* SAME weaning)
#2 TS=(protocol* SAME weaning)
#4 TS=Ventilator* Negative-Pressure
#5 TS=(mechanical SAME weaning)
#6 TS=ventilat*
#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1
#8 TS=protocol*
#9 TS=(Care SAME Manag*)
#10 TS=(Patient* SAME Management)
#11 TS=(Practice Guideline*)
#12 #11 OR #10 OR #9 OR #8
#13 #12 AND #7
#14 TS=clinical trial*
#15 TS=random*
#16 TS=placebo*
#17 #16 OR #15 OR #14
#18 #17 AND #13

Appendix 7. Data extraction form

Name of author extracting data:

Date form completed:

Study ID

Title	
Study ID for RevMan (Family name of first author and year of publication + letter if more than one per year, eg. Smith2001b)	
Are there other articles of same study? (YES, NO, Unclear. If Yes, write Study IDs)	

Study Eligibility

	(please circle)	*Source (page no. in report)*
Type of study Can the study be described as randomized?	**Yes, Unclear, No**	
Participants 1. Were the participants adults (at least18-years & over) and in ICUs? 2. Were > 80% of participants intubated (naso/orotracheal) and receiving invasive mechanical ventilation (MV)?	**Yes, Unclear, No** **Yes, Unclear, No**	
Interventions 1. Was one group weaned using a formal weaning protocol1? 2. Was the other group weaned without reference to a formal protocol?	**Yes, Unclear, No** **Yes, Unclear, No**	
Outcomes: Did the study report any one of 1. Total duration of MV (time from initiation of MV to MV discontinuation)? 2. Weaning duration (time from identification of weaning readiness to MV discontinuation)? 3. MV time prior to weaning (time from initiation of MV to identification of weaning readiness)?	**Yes, Unclear, No** **Yes, Unclear, No** **Yes, Unclear, No**	

(*Continued*)

Conclusion: Do not proceed if any of the above answers are 'No'. If study to be 'included' or 'excluded & listed in excluded table', record below the information to be inserted into tables. If included continue to page 2

Included **Excluded and should be listed in the excluded table**
Excluded and should NOT be listed in the excluded table
More information needed before inclusion decision (specify):
Record for tables:

1Protocol = a written set of rules, criteria, guidelines or algorithm for identifying readiness to wean and/or reducing ventilatory support
Source of key information

Electronic database (Which one?)	
Unpublished source (Where?)	
Personal communication (From whom?)	

Selection Bias

Method of randomization (Describe method used to generate the allocation sequence. Circle grading)	**A** Low risk **B** Unclear **C** High risk
Time of randomization (E.g. on admission, sometime prior to weaning, on decision to wean)	
Allocation concealment (Describe the method used to conceal the random allocation sequence & circle the grading)	

(*Continued*)

	A Low risk **B** Unclear **C** High risk

Detection Bias

Outcome assessor blinding (Were outcome assessors independent from the individuals administering/supervising the assigned intervention? Circle grading)	**A** Low risk **B** Unclear **C** High risk

Attrition Bias

Drop-out/withdrawals (Were any withdrawers described?)	**A** Yes **B** Unclear **C** No
Similar frequency between groups?	**A** Yes **B** No
Intention-to-treat analysis (Were participants analysed according to the intervention to which they were allocated, whether they received it or not? Please circle)	**A**. All participants entering trial **1**. 15% or fewer excluded **2**. > 15% excluded **B**. Unclear **C**. Not analysed as intention-to-treat

Quality classification

A Low risk	**B** Moderate risk	**C** High risk

Setting

Country	
Setting	Single ICU > 1 ICU (specify no.)
Type of ICU (& no.)	Medical Surgical Mixed medical & surgical unit Other (specify)

Participants

No of participants who were randomized	Intervention group n=	Control group n=
No of participants who were analysed	Intervention group n=	Control group n=
Age (mean/SD)	Intervention group	Control group
Sex of participants (M/F numbers or %)	Intervention group	Control group
Inclusion criteria		
Exclusion criteria		

Intervention Delivery

Protocolized weaning delivered by (circle all that apply)	**RNs** **RTs** **RNs & RTs** **Drs** **All** **Other** **Not specified**
Standard practice delivered by (circle all that apply)	**RNs** **RTs** **RNs & RTs** **Drs** **All** **Other** **Not specified**

Type of intervention

Readiness to wean criteria (List or circle as appropriate)	**Yes (list criteria)** **Unclear No**
Spontaneous Breathing Trial (SBT)	**Yes Unclear No** **Technique used for SBT:** (e.g. PS, T-tube, CPAP, not specified) **Length of SBT:** (e.g. 2-hour)
Stepwise reduction in support (circle type)	**Yes Unclear No** If Yes, select ONE of the following: SIMV PS Daily T-piece Intermittent T-piece Mixed (specify) Other (specify) **Unclear No**

Outcomes relevant to the review reported in paper

Total duration of mechanical ventilation (initiation of mechanical ventilation to discontinuation)	**Yes/No**
Weaning duration (identification of weaning to mechanical ventilation discontinuation)	**Yes / No**
Mechanical ventilation time prior to weaning (initiation of mechanical ventilation to identification of weaning)	**Yes / No**
Time from mechanical ventilation discontinuation to extubation	**Yes / No**
ICU length of stay	**Yes / No**
Hospital length of stay	**Yes / No**
Adverse events: - reintubation - self-extubation - tracheostomy - mechanical ventilation > 21-days - mortality - other (specify)	 **Yes / No** **Yes / No** **Yes / No** **Yes / No** **Yes / No**

Outcomes Continuous Data

Outcomes	**Unit of measurement**	**Intervention Group**			**Control Group**				**95% CI or any further details if outcome only described in text**
		n	**Mean (SD)**	**Median (IQR)**	**n**	**Mean (SD)**	**Median (IQR)**	**P value**	
Total duration of mechanical ventilation (initiation of mechanical ventilation to discontinuation)									

(*Continued*)

Weaning duration (identification of weaning to mechanical ventilation discontinuation)									
Mechanical ventilation time prior to weaning (initiation of mechanical ventilation to identification of weaning)									
Time from mechanical ventilation discontinuation to extubation									
ICU length of stay									
Hospital length of stay									

Outcomes - Dichotomous Data

Outcomes	Intervention Group (n =)	Control Group (n =)	P-value	Any further information
Reintubation				
Self-extubation				
Tracheostomy				
Mechanical ventilation > 21-days				
Mortality				

Please specify number of patients in each group experiencing the specified outcomes.

Other information which you feel is relevant to the results:

Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review.
Freehand space for writing actions such as contact with study authors and changes

WHAT'S NEW

Last assessed as up-to-date: 30 January 2010.

Date	Event	Description
20 September 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 5, 2010

Date	Event	Description
6 June 2011	Amended	We have amended the flow chart and corrected minor errors in the text We have upodated RevMan and Cochrane Handbook references.
7 March 2011	Amended	Contact details updated.
7 June 2010	Amended	We have corrected the geometric confidence intervals (CI) for hospital length of stay. Previously it read: -1% (95% CI -2% to -10%), it now reads -1% (95% CI -11% to 10%) We have been informed that the previously unpublished paper by Stahl 2009 has now been published (Stahl 2009)
29 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: B Blackwood (BB)

Co-ordinating the review: BB, F Alderdice (FA)

Undertaking manual searches: BB, P O'Halloran (POH)

Organizing retrieval of papers: BB, POH

Screening retrieved papers against inclusion criteria: BB, POH, KEA Burns (KB), FA

Appraising quality of papers: BB, POH, KB

Abstracting data from papers: BB, POH, KB

Writing to authors of papers for additional information: BB

Providing additional data about papers: BB

Obtaining and screening data on unpublished studies: BB, POH

Data management for the review: BB

Entering data into Review Manager (RevMan 5.1.2): BB, POH

RevMan statistical data: BB, CR Caldwell (CC), POH

Other statistical analysis not using RevMan: BB, CC, POH

Double entry of data: (data entered by person one: BB; data entered by person two: POH)

Interpretation of data: CC, BB, POH, FA, KB, G. Lavery (GL)

Statistical analysis: CC, BB, POH

Writing the review: BB, POH, FA, KB, GL, CC

Securing funding for the review: BB, POH, FA

Performing previous work that was the foundation of the present study: BB

Guarantor for the review (one author): BB

Person responsible for reading and checking review before submission: BB

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Nursing and Midwifery Research Unit, School of Nursing and Midwifery, Queen's University Belfast, Northern Ireland, UK.

External sources

- Research and Development Office, Northern Ireland and the Health Research Board, Ireland.

Cochrane Fellowship

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are four differences between the published protocol and the review.

1. We included quasi-randomized controlled trials, that is trials that prospectively assigned patients to groups using a quasi-random method such as alternation or hospital number. We included these studies because we felt that the rule-based system reduced investigator bias to a certain degree. Nevertheless, we assessed risk of bias in a similar manner to randomized controlled trials and conducted a sensitivity analysis excluding quasi-randomized trials.

2. We used The Cochrane Collaboration's new domain-based evaluation to assess the validity and quality of the included studies because this was released after publication of the protocol.

3. We included neurosurgical units in the subgroup analysis of type of unit as there are specific differences in weaning this group of patients because of their neurological impairment.

4. We included one further sensitivity analysis to explore the impact on the findings before log transforming the variables to approximate normality.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness; Clinical Protocols [standards]; Intensive Care Units [utilization]; Length of Stay; Randomized Controlled Trials as Topic; Respiration, Artificial [adverse effects; *utilization]; Time Factors; Ventilator Weaning [*methods]

MeSH check words

Adult; Humans